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Review

Animal models of attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) involves clinically heterogeneous dysfunctions of sustained attention, with behavioral overactivity and impulsivity, of juvenile onset. Experimental models, in addition to mimicking syndromal features, should resemble the clinical condition in pathophysiology, and predict potential new treatments. One of the most extensively evaluated animal models of ADHD is the spontaneously hypertensive rat. Other models include additional genetic variants (dopamine transporter gene knock-out mouse, coloboma mouse, Naples hyperexcitable rat, acallosal mouse, hyposexual rat, and population-extreme rodents), neonatal lesioning of dopamine neurons with 6-hydroxydopamine, and exposure to other neurotoxins or hippocampal irradiation. None is fully comparable to clinical ADHD. The pathophysiology involved varies, including both deficient and excessive dopaminergic functioning, and probable involvement of other monoamine neurotransmitters. Improved models as well as further testing of their ability to predict treatment responses are required.

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1. Introduction

1.1. General aspects of animal models of ADHD

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous neuropsychiatric syndrome of inattention, hyperactivity, and impulsivity, typically of juvenile onset [20]. Although its etiology remains unknown, modern research methods, including molecular genetics and brain imaging, have greatly expanded knowledge about this relatively common disorder. Recent advances in the study of clinical ADHD are summarized in several authoritative reviews [19,33,38,51,197,251,253,272].

For decades, basic research related to ADHD has been supported by animal models representing specific components of the clinical condition, and used to advance knowledge of the pathophysiology and therapeutics of ADHD. Animal models of ADHD include several genetic mutants, either naturally occurring or artificially produced, as well as animals prepared by brain lesioning or exposure to neurotoxins, typically early in development [89,193,227,254]. With relatively homogeneous subjects, these models allow considerable experimental control of factors that may be involved in the pathophysiology of ADHD. They also avoid complex effects of comorbidity, previous drug exposure, family interactions, and other social factors encountered in human ADHD patients.

In general, animal models should resemble a clinical disorder in as many details as possible, including symptomatic expression, treatment responses, pathophysiology, and ideally, etiology. More specifically, an adequate ADHD model should: (a) mimic the fundamental behavioral deficits found in ADHD patients (*face validity*); (b) conform to a theoretical rationale, such as the proposed pathophysiology or known therapeutics of ADHD (*construct validity*); and (c) predict unknown aspects of ADHD, such as its genetics, neurobiology, or novel therapeutics (*predictive validity*). This review considers conditions in

laboratory animals that have been used as experimental models for ADHD in the context of these criteria. Construct validity is particularly important in view of a number of recent advances in understanding the genetics and pathophysiology of ADHD.

1.2. Clinical features and biology of ADHD

1.2.1. Clinical features

ADHD is a heterogeneous syndrome that includes fundamental behavioral and cognitive features, notably, inattention, impulsivity, and variable hyperactivity [4,20]. It is diagnosed in both males and females and is typically associated with poor academic performance, though it is more often recognized in boys due to their typically overactive or disruptive behavior [4,20,101]. No clinical feature or testing procedure is specific for ADHD [4], and diagnosis is based on clinical assessment of behavior supplemented with psychological and neurocognitive evaluation.

A particularly troublesome problem is that measures of specific features of ADHD correlate inconsistently and vary substantially among individuals [18,22,216,279]. As a result, debate continues about the clinical limits of the diagnosis, and even about the basic validity of ADHD as a discrete disorder [144,239]. Social critics charge that professionals are too quick to label 'normally' energetic and exuberant children as having a 'disorder', use the label to excuse failed educational efforts, overuse stimulant treatment inappropriately, and risk stigmatization of children as mentally ill or neurologically impaired. Despite uncertainties in individual cases and some potential for abuse of the diagnosis and treatment, differences between children diagnosed as typical cases of ADHD and their peers are sufficient to sustain a clinically useful diagnostic core concept [150]. Moreover, without intervention, risks of dysfunction, disability or social impairment await many children meeting diagnostic criteria [19,20].

The apparent lack of coherence of ADHD symptoms,

and limited robustness of the diagnosis, may reflect limited measurement reliability, overemphasis on hyperactivity, and insufficient consideration of cognitive dysfunctions [18,268]. Alternatively, clinical complexity may reflect a heterogeneous pathophysiology, and environmental processes can modify specific components of brain function at distinct developmental periods to yield highly variable clinical presentations [19,33,51,85,187,192].

1.2.2. Pathophysiological hypotheses

A widely accepted hypothesis is that ADHD represents dysfunction of the prefrontal cerebral cortex of unknown cause [8,85,230]. Supporting evidence for this hypothesis includes similarities of clinical features of ADHD patients and those with injuries or diseases of the frontal lobes, as well as ADHD-like behavioral and neurocognitive deficits in animals with lesions of frontal cortex [7,9,21,27,57,72,129,168,244,292,295]. At a molecular level, the striking and consistent beneficial clinical effects of stimulant drugs in patients with ADHD, and evidence that such drugs facilitate monoaminergic synaptic neurotransmission, particularly of dopamine (DA), have strongly encouraged speculation that aberrant, and particularly deficient, cerebral monoamine neurotransmission may contribute to the pathophysiology of ADHD [17,89,197,235]. However, the hypothesis that ADHD is associated with deficient DA transmission has limited and inconsistent direct experimental support by clinical metabolic studies and findings of brain-imaging studies considered below.

Some support for a role of DA in the pathophysiology, and especially the therapy, of ADHD comes from studies of DA and its metabolites in the body fluids of ADHD patients [52,53]. Notably (and probably circularly) hyperactive behavior and superior responses to stimulant treatment in ADHD patients have been associated with elevated cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA), a principal metabolite of DA. Additional complex findings that are not readily interpreted derive from use of computed positron emission tomography (PET) of the brain. This functional imaging technique has demonstrated *increased* uptake of the labeled DA precursor [^{18}F]-L-dopa in the midbrain of some adolescents with ADHD [83], but *decreased* uptake in the prefrontal cortex (PFC) of adult ADHD patients [82]. Additional functional brain-imaging studies comparing ADHD patients and normal controls have labeled the DA transporter (DAT) protein, a specific marker for DA neurons, with nonhydrolyzable phenyltropane analogs of cocaine. These DAT radioligands include [^{131}I]altropane [75] for PET, and [$^{99\text{m}}\text{Tc}$]TRODAT-1 and [^{131}I]β-CIT for single photon emission computed tomography (SPECT) [75,76,146,281]. All but one study involving these radioligands [281] found *increased* binding to DAT in the DA-rich basal ganglia of ADHD subjects. However, again, the correct interpretation of these observations is far from

clear. They may reflect increased abundance or tissue density of DA nerve terminals, or an increase in DAT-per-neuron, perhaps with a net reduction of synaptic availability of DA, and artifacts due to previous treatment are not entirely excluded. In addition, improvement in clinical symptoms with d,l-methylphenidate was associated with decreased DAT binding [76,146]. This effect evidently reflects the ability of this stimulant, and perhaps released DA, to compete for DAT binding sites with the radioligands employed, and not necessarily evidence that stimulants alleviate ADHD symptoms by correcting an underlying abnormality in DA neurotransmission.

A role of norepinephrine (NE) in ADHD is suggested by the effectiveness of tricyclic and other antidepressant drugs that are selective inhibitors of the NE-transporter (NET) [32,33,198], as well as α_2 -adrenergic agonists [127,128,231], in alleviating clinical symptoms of the disorder. A role of serotonin (5-hydroxytryptamine; 5-HT) neurotransmission in clinical ADHD is less secure since serotonin-selective reuptake inhibitors (SRIs) have limited benefit in ADHD patients [20,26,51,198]. Nevertheless, 5-HT is implicated in both the pathophysiology and pharmacology of several ADHD models reviewed below.

1.2.3. Genetic hypotheses

ADHD has been linked to polymorphisms of several genes implicated in monoamine neurotransmission [194,275], including the DA transporter (DAT1) [63] and D_4 receptor (DRD4) genes [151]. ADHD was associated with polymorphism of DAT1 in some studies [63,105,266], but not others [214,276], and the associated alleles may be particularly effective in transporting DA into nerve terminals [95,113,164,171,175].

The D_4 receptor gene (DRD4) is located in the short (p) arm of human chromosome 11, at position 11p15.5 [282]. The greatest variance in peptide sequence from other DA receptors occurs in the third intracellular sequence of this peptide, which is required for interaction with G proteins and second-messenger signaling [282]. An association between ADHD and a relatively long, 7-repeat allele (DRD4.7), involving a repeating 48 base-pair (16-amino acid) sequence that affects the length of the third intracellular loop, was first identified by La Hoste and colleagues in 1996 [151]. This linkage has been confirmed by most [23,86,247,269], but not all, later studies [78,111,277], and meta-analysis of these results supported a significant but modest association with ADHD [87]. The same $D_{4,7}$ genotype was also associated with personality traits related to ADHD, including novelty-seeking and impulsivity [29,77]. The $D_{4,7}$ receptor is considered less sensitive to DA and less efficient than other forms of D_4 receptor in transducing DA-stimulated intracellular signals, such as inhibition of adenylyl cyclase [13]. Such findings encourage speculation that beneficial effects of stimulants may include indirect activation of hypofunctional cerebral D_4 receptors in ADHD patients.

Candidate genes of the NE neurotransmission system also have been considered in ADHD [33,301,302]. Barr and colleagues [25,299] tested genes encoding two α -adrenoceptors, α_{1C} (ADRA1C; located in the short arm of human chromosome 8, at 8p11.2) and α_{2C} (ADRA2C; at 4p16). With transmission dysequilibrium analysis, they found no biased transmission of any known allele of these genes, and concluded that the alleles considered were not linked to ADHD in the families tested.

Encouraged by findings that nicotinic acetylcholine (ACh) receptor agonists can improve attention, learning, and memory in ADHD patients [153,286,291], the α_4 nicotinic receptor gene (CHRNA4) was studied in 70 family samples involving children with ADHD, with no evidence of an association with ADHD [141].

1.2.4. Neurodevelopmental hypotheses

Studies of obstetrical complications as contributing factors for ADHD have yielded conflicting results. Compared to normal controls, children with ADHD were found to have had a higher incidence of perinatal hypoxia [159,259]. However, associations of ADHD with other perinatal complications, including toxemia, older maternal age, and premature birth, have been inconsistent and remain inconclusive [303].

A developmental defect leading to anomalous symmetry or interhemispheric connectivity of the brain has also been considered in ADHD [92,100]. Reduced size of the corpus callosum, particularly in its rostral or splenial portion, has been detected in some children diagnosed with ADHD [28,163], and the typically larger corpus callosum in the human female brain [125,134] may be protective against ADHD [6,101]. However, a direct link between ADHD and defective transfer of information between the cerebral hemispheres has not been demonstrated in ADHD. Moreover, substantial callosal hypoplasia usually is associated with other major neurodevelopmental disorders that are not specifically associated with ADHD [294].

Recently, the cerebellum has been implicated in cognition and emotion, in addition to its traditional role in coordinating movement and maintaining body posture during ambulation [91,152], suggesting a possible contribution to ADHD that is consistent with reports of deficits in fine motor control in some ADHD patients [31,110,289]. As the primary site for memory consolidation, the hippocampal formation is also of potential interest in ADHD. Structural brain imaging has not revealed evidence of structural abnormality of the hippocampus [54,92], but functional imaging has found reduced cerebral glucose metabolism in this brain region in adolescent girls with ADHD [80,81].

1.2.5. Toxicological hypotheses

Studies of hypothesized dietary factors, including excessive ingestion of sucrose, have yielded mainly negative results, but other environmental toxins have been impli-

cated in ADHD. Lead exposure during development can produce various nonspecific neurobehavioral abnormalities, including hyperactivity, restlessness, distractibility, and impaired cognition. However, lead contamination is not found in most cases of ADHD [185,186]. Parents of ADHD children may consume more alcohol and tobacco than parents of normal controls [65], and exposure to alcohol or tobacco smoke during early development may be a risk factor for ADHD [173,263,264].

2. Laboratory models of ADHD

2.1. Genetic models

2.1.1. Spontaneously hypertensive rat

In the early 1960s, the spontaneously hypertensive rat (SHR) was developed in Japan by inbreeding rats of the Wistar-Kyoto (WKY) strain [188]. Selecting for hypertension also yielded unexpectedly high spontaneous motor activity [179]. Over several decades, Sagvolden and colleagues [227–229] at the University of Oslo studied the SHR extensively and established it as one of the most widely used animal models of ADHD.

SHR shows several features characteristic of ADHD [179,227], including motor hyperactivity in a novel environment, excessive responses under a fixed-interval/extinction schedule, and difficulty in acquiring operant tasks [178,227,297,298]. These behavioral abnormalities correspond to the clinical features of hyperactivity, impulsivity, and learning deficit, respectively. Hyperactivity and impulsivity in SHR was attenuated by agents that potentiate monoaminergic neurotransmission, including amphetamine and the monoamine oxidase (MAO) inhibitor selegiline ([–]-deprenyl) [36,182]. Also similar to patients with ADHD [228], the SHR is more sensitive to immediate behavioral reinforcement and less sensitive to delayed reinforcement than are nonhypertensive WKY control rats [229]. These similarities strongly support the face validity of the SHR as an animal model for ADHD. However, other features are discordant, notably, a lack of sex-differences in SHR [30].

The behavioral and cognitive abnormalities in SHR are also responsive to stimulants, including d-amphetamine and d,l-methylphenidate [182,229], adding to the construct validity of SHR as a model of ADHD. In a two-compartment test setting with a home area freely accessible to a contiguous open field, SHR spent most of test sessions in the open field, whereas normal WKY rats preferred the home area [298]. Low to medium doses of methylphenidate moderately increased activity of SHR, but induced intense motor hyperactivity in WKY rats. At high doses, methylphenidate reduced locomotion and rearing in both SHR and controls, apparently due to emergence of stereotyped behavior [298]. Similar to their clinical effects in ADHD, stimulants weakened the influence of immediate

reinforcers on behavior, and strengthened that provided by delayed reinforcers, although these effects were less pronounced in SHR than in WKY controls [229].

Blunted responses of SHR to stimulants seem to be mediated by impaired release of DA from nerve terminals in prefrontal cerebral cortex (PFC), nucleus accumbens, and caudate-putamen [72,139,183,217,219–221]. In addition, metabolic turnover of DA (indicated by the ratio of its metabolites to DA) in the neostriatum (bilateral) and nucleus accumbens (right side only) of SHR was less than in control WKY rats [36]. Amphetamine increased release of DA more than methylphenidate in SHR brain tissue, presumably reflecting its greater effect on intraneuronal vesicular storage, in addition to effects on DA reuptake of both agents [220]. This finding may suggest an abnormality in vesicular storage of DA in SHR.

In addition to abnormal presynaptic DA transmission, molecular indices of postsynaptic neurotransmission in brain, including activity of Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), and expression of the immediate early genes *c-fos* and *zif-268* also were lower in SHR than in normal WKY rats [191,223]. Interestingly, CaMKII levels normalized with repeated daily treatment of SHR with methylphenidate [191]. Young, pre-hypertensive, male SHRs had increased tissue concentrations of D_1 or D_2 receptors in rostral neostriatum, accumbens, and olfactory tubercle, presumably secondary to deficient stimulation by DA. The receptor changes normalized with repeated methylphenidate treatment [48]. These findings are consistent with the view that stimulants alleviate ADHD symptoms by correcting deficient dopaminergic neurotransmission.

Increased NE transmission also has been detected in the SHR. NE uptake by synaptosomal preparations of cerebral tissue of SHR was greater than in WKY rats in all brain areas tested [183], suggesting decreased noradrenergic function. Increase NE reuptake was not a direct result of high blood pressure since it was found before hypertension emerged. However, in the PFC, NE release in response to glutamate was increased in comparison to control WKY rats [222]. Inhibition of NE release by the α_2 autoreceptor may also be deficient in SHR [218], leading to overall increased NE transmission, and presumably affecting blood pressure as well as behavior. Indeed, hypertension is a potential confounding factor for SHR as a model for ADHD. Many behavioral deficits in SHR, especially those related to learning and memory, might reflect brain dysfunction or damage caused by high blood pressure. Also, whether beneficial effects of drugs such as the α_2 -adrenergic agonists clonidine and guanfacine in this model as well as in clinical ADHD, reflect direct central neuropharmacological effects of these agents, or lowered blood pressure, remains uncertain [89,227,298].

In an effort to separate hyperactivity from hypertension, Hendley and her colleagues at the University of Vermont selectively bred hypertensive-only (WKHT) and hyperacti-

ve-only rats (WKHA) by crossbreeding SHR with WKY rats [114–116]. In WKHA rats, prominent behaviors include hyperactivity in a novel environment and increased reactivity to stress, both of which are also characteristic of SHR [114–116]. However, WKHA rats are less aggressive than classic SHR, and habituate more readily to a novel environment [114,116]. In addition, the uptake of DA in WKHA brain tissue was significantly greater than in the hypertensive strains (WKHT and SHR) [115], tending to implicate altered DA transmission in the trait of hyperactivity rather than in hypertension. In contrast, increased neuronal uptake of NE, which was specific to SHR and WKHT strains only, and was not found the hyperactive WKHA rats [115], suggesting that altered NE neurotransmission may contribute to hypertension rather than hyperactivity.

2.1.2. Dopamine transporter knockout mouse

The neuronal reuptake process mediated by neuron-specific monoamine transporter proteins in neuronal membranes is the primary mechanism for close control over synaptic signaling by monoamine neurotransmitters [93,98]. Stimulants inhibit or reverse the functioning of the DA transporter (DAT), and exert additional effects on NE (NET) and 5-HT transporters (SERT), as well as variable effects on presynaptic vesicular uptake and storage processes [147,148]. Increased DA transmission in the basal ganglia and limbic forebrain is believed to underlie behavioral activation induced by stimulants [56]. Genetically engineered 'knockout' (*DAT-KO* or *DAT*^{-/-}) mice lack functional DAT and demonstrate striking spontaneous behavioral hyperactivity compared to wild-type (*DAT*^{+/+}) mice during both light and dark phases of the daily cycle [97,99,106]. The half-life of behavioral habituation in homozygous *DAT*^{-/-} mice was over twice that of heterozygous (*DAT*^{+/-}) littermates (90 vs. 40 min), and much longer than in wild-type mice. *DAT-KO* mice also showed significant cognitive impairment in an eight-arm radial maze, a standard test of spatial learning [97,99]. Further behavioral analysis demonstrated no apparent deficits in social behavior [258].

Robust behavioral hyperactivity in *DAT-KO* mice was associated with an approximately 300-fold decrease in the rate of clearance of extracellular DA, as measured by cyclic voltammetry in brain striatal slices [137]. Profound, evidently compensatory, changes also occur. They include decreases in tissue content (by 95%) and release of DA (by 75%) from nerve terminals [98,137]. As a result, extracellular DA concentration was increased only by 5-fold despite complete loss of DAT in homozygous *DAT-KO* mice. DA metabolites have, variably, been either increased (HVA), or unaltered (3,4-dihydroxyphenylacetic acid [DOPAC]) in the *DAT-KO* mouse [137]. Synthesis of DA (at the rate-limiting step of L-tyrosine hydroxylation) was increased as measured by accumulation of L-dopa follow-

ing inhibition of L-aromatic amino acid decarboxylase, apparently due to allosteric modulation of tyrosine hydroxylase (TH) activity [130,131,137]. Increased TH activity is thought to reflect loss of tonic inhibition of TH by DA in nerve terminals, as well as an unexplained loss of negative feedback control of TH activity by presynaptic D_2 autoreceptors that may involve dysregulated activation of TH by phosphorylation [106,136]. Despite these profound functional alterations at DA terminals, anatomical abnormalities of DA neurons have not been found, even at the electron-microscopic level [97,98,106].

In addition to adaptive presynaptic changes in DA neurons, postsynaptic D_1 and D_2 receptors were also significantly down-regulated in DAT-KO mice, with approximately 50% decreases in both their mRNA and protein levels in basal ganglia [98,130,131]. These changes are quantitatively unprecedented, and seem to be directed toward restoring functional homeostasis of dopaminergic neurotransmission disturbed by loss of DAT [136,137]. Levels of the mRNA for preproenkephalin-A (possibly under inhibitory control by D_2 receptors) was substantially reduced, whereas the message for dynorphin (responsive to stimulation by D_1 receptors) significantly increased [106].

Behavioral hyperactivity in DAT-KO mice can be inhibited by amphetamine, methylphenidate, and cocaine [97,98,138]. Since DAT is a primary molecular target of stimulant drugs, these findings seem counter-intuitive. Also inconsistent with the view that behavioral effects of stimulants are mediated primarily by DA neurotransmission is the finding that DA concentrations in neostriatum of DAT-KO mice did not increase with challenges with these drugs or with environmental novelty [97–99], although a relatively intact DA system seemed necessary for the behavioral effects of stimulants [99]. 5-HT seemed to be a prime candidate for such pharmacological effects since the motor hyperactivity in DAT-KO mice was also antagonized by the 5-HT releasing agent fenfluramine, the SRI antidepressant fluoxetine, and the 5-HT agonist quipazine [99]. Moreover, pharmacological depletion of 5-HT abolished the antihyperactivity action of fenfluramine. NE also may be involved since behavioral responses to amphetamine and cocaine were mimicked by selective inhibitors of NET but not of DAT [45].

DAT-KO mice also show other abnormalities not found in ADHD, including growth retardation and premature death. By 10 weeks of age, survival is only about 68% in homozygotes vs. 97% in wild-type controls [98,106]. DAT-KO mice can reproduce, but females show impaired maternal behavior, and their young require cross-fostering by normal dams to survive [37,98]. Changes in reproductive behavior are paralleled by loss of prolactin-producing cells in the anterior pituitary, and depressed functioning of the hypothalamus [37,96].

2.1.3. Coloboma mutant mouse

The coloboma mutant mouse was produced by neutron

irradiation, and only the heterozygote ($Cm^{+/-}$) is viable [234]. $Cm^{+/-}$ mouse shows a variety of behavioral deficits that resemble core features of ADHD, including pronounced spontaneous motor hyperactivity, and delayed neurodevelopmental milestones [117,119,121,293]. On average, these mutants are three-times more active than normal controls, with considerable individual variation [118,119,121]. Hyperactivity in coloboma $Cm^{+/-}$ mouse was reduced by low doses of d-amphetamine (2–4 mg/kg). In contrast, methylphenidate (2–32 mg/kg) increased locomotor activity in both the mutants and normal controls in a dose-dependent manner [118].

Behavioral changes in coloboma mouse are associated with a mutation of the gene encoding SNAP-25, a synaptosome-associated protein of 25 kDa molecular mass [118,119,262]. As a key component of the synaptic vesicle-docking-and-fusion process that is essential for exocytotic release of catecholamines and other neurotransmitters, SNAP-25 forms a stable ternary complex with the synaptic proteins syntaxin-1a and VAMP-2 (synaptobrevin-2). Mutation of SNAP-25 leads to profound disruption of dopaminergic neurotransmission. DA release induced by neuronal depolarization is almost completely lost in the dorsal, but not ventral, striatum of this mouse, and somewhat augmented in its cerebral cortex [203]. These regionally selective functional deficits in DA release may underlie the behavioral hyperactivity observed in this mutant, and changes in hippocampal physiology may contribute to impaired information processing also found in this model [293]. In addition to changes in DA systems, increased concentrations of NE also were found in striatum and nucleus accumbens of the coloboma mutant [135].

In an effort to identify a possible contribution of SNAP-25 in human ADHD, Hess and colleagues examined polymorphic markers in the region of chromosome 20 syntenic to coloboma (20p11–12) in five human pedigrees, in which inheritance of ADHD appeared to be best explained by a sex-influenced, single-gene, Mendelian model [120]. They found no linkage between the disease and markers near the SNAP-25 gene locus. Another clinical genetic study used single-stranded conformational polymorphism-analysis (SSCP) to determine DNA sequences in the 3'-untranslated region of the human SNAP-25 gene [24]. Two polymorphisms were identified in this region by use of restriction enzymes. Transmission of the alleles for each polymorphism and their haplotypes were examined by transmission disequilibrium in 97 families of ADHD probands, their parents and siblings. Biased transmission of the haplotypes of the alleles of both polymorphisms was found, suggesting a role of the SNAP-25 gene in ADHD.

2.1.4. Naples high-excitability rat

Naples high-excitability (NHE) rat is another genetic animal model of ADHD that may involve excessive DA functioning in limbic and cortical areas of forebrain

[14,108,190,191,224,225]. The NHE strain is hyperexcitable and shows deficits in tasks requiring visuospatial attention [14,191]. The high reactivity of NHE rats to novelty is not based on generalized hyperactivity, since their 24-h spontaneous motor activity did not differ significantly from that of random-bred controls (NRB), or a low-excitability (NLE) strain. Responses of NHE rats to stimulants remain to be evaluated fully.

Based on immunocytochemical analysis, NHE rats, compared to NRB controls, had larger DA neurons and higher TH content in the ventral tegmental area (with cell bodies of the mesolimbic DA system), but not in substantia nigra (origin of the nigrostriatal DA system) [224,283]. These findings suggest that increased behavioral activity and impaired attention of NHE rats may be associated with hyperfunctioning of the mesocorticolimbic DA system.

2.1.5. Acallosal mouse strain I/LnJ

The inbred acallosal mouse strain I/LnJ shows total callosal agenesis with complete penetrance, with behavioral features resembling ADHD, including impaired acquisition in conditioned learning tasks [156,157,165]. Among mice produced by crossing I/LnJ with normal wild-type C57BL/6 mice, those with $\geq 88\%$ of alleles of the I/LnJ strain were hyperactive in an open field, with considerable individual variability [165]. Acallosal mouse also showed fewer brief stops and spent more time in the center of the open field at the beginning of the session. Time spent in the center of an open field was associated with lower uptake of radiolabeled 2-deoxyglucose in left striatum and cerebral cortex, whereas brief stops correlated with bilaterally lower metabolic activity in frontal and parietal cortex [165]. These observations suggest that behavioral hyperactivity in this callosal agenesis model is related to functional dominance of the right hemisphere that may be exaggerated by the lack of callosal connections. Interestingly, specific dysfunction of the right cerebral hemisphere is also suggested to occur in clinical ADHD [100,261], although there is no evidence of either malformation or dysfunction of the corpus callosum in brains of ADHD patients.

The relationship of callosal agenesis to behavioral disinhibition in the acallosal mutant mouse may be further clarified by comparing behavior in mice with variably sized corpora callosa, as well as with acallosal animals with different genetic backgrounds [285]. Status of neurotransmitter function and effects of stimulants remain to be tested in acallosal mice as a potential animal model of ADHD.

2.2. Neurotoxin-exposed animals

2.2.1. Juvenile rats with neonatal 6-hydroxydopamine brain lesions

Extensive lesioning of DA neurons in adult animals results in behavioral deficits characteristic of Parkinson's

disease, including bradykinesia, sensory neglect, aphagia and adipsia [166,280,308]. In contrast, selective removal of DA projections to forebrain in neonatal rats leads to age-limited spontaneous motor hyperactivity [64,112,160,162,242,243], without gross deficits in sensorimotor function [44,248,287]. Hyperactivity in the model is most prominent at an age corresponding to human periadolescence [79,243,307], and is dose-dependently antagonized by stimulants [67,112,162,242]. As a result, juvenile rats with neonatal DA lesions are widely used to model ADHD and its treatment.

Neonatal DA lesioning also results in loss of sensitivity to the intoxicating effects of ethanol and diazepam [84]. These findings may have clinical relevance since ADHD is a risk factor for alcohol abuse and antisocial behaviors [19,20,110]. In addition, the neonatally lesioned rat shows deficits in learning and memory, as suggested by impaired acquisition of spatial discrimination tasks and operant responses [5,241,271,288]. Learning deficits can be detected as early as 48 h after neurotoxin treatment, reach maximal levels soon after weaning, and typically disappear by adulthood. Similar to responses of motor behavior to stimulants, learning deficits induced by neonatal DA lesions also respond favorably to stimulant treatment. Thus, deficits in conditioned learning based on olfactory cues in these rats were alleviated by amphetamine [296], and T-maze learning was improved by methylphenidate [241].

Sparing of sensorimotor functions after neonatal DA lesioning, and the age-limited behavioral deficits that follow such lesioning, may reflect ability of young animals to repair or regenerate DA neurons after insults. Late, unilateral lesioning of the nigrostriatal DA projection in adult rats following neonatal lesioning with 6-OHDA produced contralateral sensorimotor deficits, suggesting that regeneration of DA neurons may be sufficient to restore motor functions in adult rats with neonatal lesions [208]. Adaptive functional changes in the remaining DA neurons are also indicated by increased DA release from terminals [46,50], and increased TH mRNA and protein levels in cell bodies [34,140]. Compensatory mechanisms tending to restore DA transmission also include loss of presynaptic D_2 autoreceptors that normally inhibit the firing of these neurons, and of DAT that normally removes DA from the synaptic cleft [140,232].

In addition to presynaptic changes in DA transmission, postsynaptic mechanisms are also altered after neonatal DA lesions. Sensitivity of D_1 receptors to agonists is increased, with decreased response to D_1 antagonists. Altered D_1 receptor sensitivity is strongly implicated in L-dopa-induced self-injurious behavior in neonatally lesioned rats [39–42]. In contrast, neonatally lesioned rats are less sensitive to D_2 antagonists such as haloperidol, whereas rats lesioned with 6-OHDA in adulthood are exquisitely sensitive to such drugs, again suggesting that adaptive responses of DA receptors to loss of DA during

early development are fundamentally different from those induced by DA lesions in adulthood [140].

Loss of DA during early development also leads to profound adaptations in the 5-HT system. These include substantial, regionally-selective, and sustained 5-HT hyperinnervation of striatum [71,94,145,161,260,278,305]. Quantitative immunocytochemistry revealed increased tissue content of 5-HT associated with proliferation of 5-HT nerve terminals [278]. However, the functional significance of 5-HT hyperinnervation of the striatum remains unclear. The increase of 5-HT fibers after lesioning did not interfere with outgrowth of DA-containing fibers arising from transplanted DA cells, nor did such transplantation in neonatal brain prevent 5-HT hyperinnervation after 6-OHDA lesioning [250]. Another important finding is that rats with early lesions to both DA and 5-HT systems (produced with 6-OHDA plus 5,7-dihydroxytryptamine) did not exhibit symptoms characteristic of Parkinson's disease [44], suggesting that 5-HT does not compensate for the loss of DA to maintain motor functions. Furthermore, hyperinnervation by 5-HT in striatum did not occur if 6-OHDA lesions were carried out at later ages (e.g. at postnatal days [PD] 15–27), yet such preweaning and adolescent-lesioned rats were devoid of major motor deficits [140].

In contrast to adaptive changes in the 5-HT system, development of the central NE system seems to be normal in rats with neonatal 6-OHDA lesions [161,189]. Moreover, an intact NE system is necessary for the antihyperactivity effects of stimulants that potentiate the release NE as well as DA [147,148]. Indeed, amphetamines, including d-amphetamine, d-methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA), release NE more potently than DA [215]. Moreover, the calming effects of stimulants can be mimicked by selective inhibitors of NET such as desipramine and nioxetine, but not by selective inhibitors of DAT such as GBR-12909 and amfonelic acid [68]. These findings parallel compelling evidence of clinical benefits in ADHD of selective inhibitors of NET including desipramine, nortriptyline, and atomoxetine [32,33,198,257]. Mechanisms by which inhibitors of NET alleviate hyperactivity remain unknown, but they may include α -adrenergic enhancement of prefrontal cerebral cortical functioning [10–12,16,158].

The well-established normalization of motor hyperactivity as neonatally lesioned rats reach adulthood is particularly intriguing. Re-innervation of the neostriatum by DA-rich cell transplants limits hyperactivity [46,47]. Normalization of motor behavior in neonatally 6-OHDA-lesioned rats correlated with gradual recovery of DA innervation in nucleus accumbens, but not caudate-putamen [307], as quantified by transporter autoradiography using a selective DA transporter radioligand [149].

D₄ receptor plasticity also may contribute to behavioral hyperactivity in this model. First, motor hyperactivity in neonatally 6-OHDA-lesioned rats correlated with substan-

tial increases in levels of D₄, but not other DA receptors, in caudate-putamen [306]. Second, lesion-induced motor hyperactivity was dose-dependently inhibited by several D₄ receptor-selective antagonists, but not by D₂/D₃ antagonists [304,306]. Third, increased D₄ receptor binding in forebrain tissue of lesioned rats was detected only in early development when hyperactive behavior was pronounced, but not later when motor activity returned to control levels [307]. Since D₄ receptor polymorphism has been repeatedly linked to ADHD (see Section 1.2.3.), these findings strongly suggest that abnormal development of the D₄ receptor might contribute to hyperactivity in ADHD patients and that D₄-selective antagonists may represent a much needed, novel treatment for ADHD.

2.2.2. Neonatal hypoxia in rats

In rats, cerebral hypoxia induced by 25 min of immersion in 100% nitrogen at 30 h after birth leads to behavioral abnormalities with some similarities to ADHD [70,255,256]. These include age-limited hyperactivity in an open field that is most prominent at PD 20–45, and permanent deficits in learning and memory [109]. Treatment with d-amphetamine can counteract the hyperactivity, but stimulants have not been adequately tested for effects on learning and memory in this model [256].

Neonatal hypoxia results in complex alterations in the central monoamine systems that change with age [70]. Initially, at 20 min post-anoxia, levels of NE in cerebral cortex, DA in striatum, and levels of their metabolites were reduced, whereas tissue concentrations of the principal 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) were increased in cerebral cortex and cerebellum [70]. In contrast, 1 week later, NE was increased in cerebellum, and both 5-HT and 5-HIAA levels were decreased in cortex and cerebellum. By PD 21, hippocampal NE and striatal HVA levels were increased, striatal 5-HT decreased, with increased 5-HIAA in both striatum and hippocampus, and at PD 60, striatal levels of DOPAC and 5-HIAA were increased [70]. Possible relationships of these complex metabolic changes to the neurobehavioral manifestations in the model, let alone to the pathophysiology of clinical ADHD, remain to be investigated.

Neonatal hypoxia in rats also produces long-lasting morphological change in hippocampus [69]. Neuronal density was reduced selectively in CA1 at PD 15 and later, but an index of neural repair, fibrillary staining in astroglia, increased as early as PD 7 [69]. The number of neurons showing immunoreactivity for the immediate early gene *c-fos* was also decreased in hippocampal CA₁, CA₂, and CA₃ regions [69]. These findings suggest that hippocampal damage may contribute to deficits in learning and memory typical of neonatally hypoxic rats.

2.2.3. Developmental cerebellar stunting in rats

Neuroanatomical and functional effects of insults to the immature cerebellum vary with age and the state of neural

development. Very early surgical lesions of the cerebellum or exposure to toxins at PD 1–4 produce severe changes in cerebellar morphology, with ataxia and tremor, and generally reduced activity with poorly coordinated movements, as well as some deficits in learning and memory. Similar insults only a few days later (PD 5–12) cause less severe neuropathology, with motor hyperactivity and minor learning deficits that simulate ADHD [88–90].

The antimitotic agent methylazoxymethanol acetate, given to rats at PD 5–8, permanently reduced cerebellar weight with relatively minor effects in other brain regions [88,90]. This treatment produced mild hyperactivity in open field and running-wheel tests that was more pronounced in males, without gross deficits in learning tasks. Also, treatment of rats with the synthetic glucocorticoid dexamethasone during early development caused permanent reduction in cerebellar weight and mild behavioral hyperactivity, again mainly in male rats, without gross learning deficits [89]. Finally, oral administration of all-*trans*-retinoic acid to pregnant rats resulted in decreased cerebellar weight and hyperactivity in a running wheel test in their offspring [126].

These observations suggest that some features of ADHD can be simulated by early cerebellar damage in the rat. However, more detailed analyses of behavioral consequences of such damage and effects of stimulants are needed to establish animals with early cerebellar damage as valid models of ADHD. Moreover, there is no basis to implicate cerebellar damage or dysfunction in clinical ADHD.

2.2.4. Exposure of animals to environmental toxins

Exposure to environmental toxins including lead and polychlorinated biphenyls (PCBs) might contribute to occasional cases of ADHD [226,240]. Mice chronically exposed to inorganic lead from birth demonstrated markedly increased levels of spontaneous motor activity compared to normal control, that was reduced by treatment with amphetamine and methylphenidate [245,246]. In addition, early exposure of rats to PCB congeners (IUPAC 118, 126 and 153) in utero or through mother's milk has led to impaired visual discrimination and slight motor hyperactivity [123,124]. Rats exposed to PCB-153 as pups also showed behavioral changes indicative of impulsivity such as rapid lever-pressing immediately before a reinforcer became available in an operant task [123,124]. No abnormalities were found in the size, weight, or gross physical development of these rats. Monkeys exposed to lead or PCBs during early development have also shown deficits in both spatial and non-spatial learning tasks, as well as impulsive behaviors in certain operant schedules [210–212].

Mechanisms responsible for behavioral and cognitive abnormalities in animals exposed to PCBs or lead early in life are unknown. In forebrain tissue of mice exposed to lead early in life, a synaptosomal fraction showed in-

creased high-affinity transport of L-tyrosine, and decreased uptake of choline and DA, with increased tissue levels of NE, but not DA or acetylcholine [245,246]. At a symptomatic level, behavioral deficits produced by lead and PCBs are consistent with damage to PFC [154,209], although such effects have not yet been demonstrated.

2.2.5. X-ray damage of hippocampus in rats

Exposure of rat pups to X-irradiation results in a number of behavioral deficits that resemble features of clinical ADHD [66,73,74], even though ionizing radiation is very unlikely to be a significant contributor to human ADHD. Changes produced by early exposure to X-rays include profound hyperactivity and deficits in learning and memory without gross deficits of sensorimotor function [2,3,102,122]. Learning and memory deficits in such early-irradiated rats can be alleviated with d-amphetamine [122]. Behavioral changes in this model may be due to reduced populations of interneurons in forebrain, especially in hippocampus [2,3,102]. A prominent role of hippocampus in this model is also suggested by ADHD-like symptoms such as hyperactivity in rats with focal irradiation of the brain [74].

2.3. Miscellaneous models

2.3.1. Hyposexual male rats

Sexual behavior in rodents is maintained by circulating concentrations of androgenic steroids and levels of their receptors in the preoptic area of brain, and is triggered by external stimuli including the sight, smell, and touch of a receptive female. A high proportion of male rats that fail to copulate with receptive females in a standard environment are hyperactive [142,143]. These rats also show other behavioral features suggestive of ADHD, including overactivity and impulsivity in open field testing, diminished hyperactivity in response to d-amphetamine, and decreased ability to ignore irrelevant information in a conditioned avoidance test [35,142,143].

2.3.2. Animals selected from a general population

Behavioral deficits in the animal models already described are typically induced by a variety of invasive procedures that are unlikely to be encountered in human ADHD patients. Using the five-choice serial reaction time task (5-CSRTT), Puumala and colleagues found that some apparently normal Lister hooded rats tend to show attention deficits and impulsivity [199–201]. The testing paradigm resembles methods commonly used to assess vigilance and sustained attention in human subjects, and requires animals to discriminate a brief visual stimulus presented randomly in one of five locations, and to respond appropriately with a nose-poke to receive reinforcers. In addition to its spontaneous nature, an attractive feature of this model is its focus on sustained attention that is rarely examined in other models. Sustained attention is scored for

accuracy (percent correct responses) and impulsivity (percentage of premature responses). Deficits in the poor-performers were not due to visual impairment, since increasing stimulus intensity or duration did not preferentially affect poor-performers [201]. Also, no relationship was observed between choice-accuracy and latency to collect reinforcers after correct responses, indicating that motivational factors do not underlie the attention deficit or pervasive responses of poor-performers.

Following training of rats in the 5-CSRTT paradigm, tissue from selected brain regions was assayed for monoamines and their metabolites [202]. A measure of metabolic turnover of serotonin (5-HIAA/5-HT ratio) in left frontal cortex correlated inversely with choice-accuracy, whereas DA turnover (DOPAC/DA) in right frontal cortex correlated positively with performance. Premature responses, on the other hand, correlated with 5-HT turnover in right frontal cortex. These findings indicate that DA and 5-HT in frontal cerebral cortex play an important role in the modulation of attention and response control.

The 5-CSRTT behavioral testing procedure not only provides a unique model to simulate attention deficits in ADHD, but has also yielded information on the regulation of sustained attention. Consistent with a prominent role of the central cholinergic system in cognition, choice-accuracy is severely compromised in rats with selective lesions to the nucleus basalis of Meynert [180,181]. Destruction of the mesolimbic DA projection increased response-latency in the 5-CSRTT paradigm, and decreased overall responding, with no apparent effect on choice-accuracy [61], indicating a change in motivation rather than attention. Lesions of NE system, on the other hand, disrupted 5-CSRTT performance only when distracting stimuli were present or target stimuli become temporally unpredictable [60], suggesting that NE transmission serves to direct attention to goal-directed events.

3. Discussion

A summary of animal models of ADHD, with salient similarities to and differences from the clinical disorder, is provided in Table 1.

3.1. Monoaminergic functions in animal models of ADHD

3.1.1. Dopamine

In SHR, behavioral deficits analogous to ADHD symptoms are usually considered to be mediated by an impaired DA reward mechanism that consists mainly of dysregulation of DA release, although changes in postsynaptic responses to DA also have been detected (see Section 2.1.1.). Rats with neonatal 6-OHDA lesions represent another model with decreased DA transmission (see Section 2.2.1.). Despite losses of DA that are similar to those

in bradykinetic rats with adult 6-OHDA lesions, neonatally lesioned rats display a robust motor hyperactivity that is inhibited by stimulant drugs, but not by selective inhibitors of DA transport. Behavioral deficits in coloboma mutant mice are caused by a mutation of the SNAP-25 gene, with a resulting deficiency in DA transmission (see Section 2.1.3.). In striking contrast to SHR, rats with neonatal 6-OHDA lesions, and coloboma mice, the DAT-KO mouse is a model with a completely opposite underlying pathophysiology, namely persistent hyperdopaminergic function (see Section 2.1.2.).

The similarity of behavioral and pharmacological profiles of animal models of ADHD based on deficient DA transmission and those with increased DA transmission is paradoxical. As a step toward rationalizing this paradox, we propose that an appropriate, intermediate, level of activity of cerebral catecholamine systems, especially of DA transmission, is essential to maintain normal responses and adaptations to environmental stimuli. Animal models with decreased DA transmission, such as SHR and the neonatally 6-OHDA lesioned rat, and those with increased DA transmission, such as the DAT-KO mouse, represent deviations from an optimal level, albeit in opposite directions. In models with diminished DA transmission, stimulants may be beneficial by enhancing release of DA. In models with excessive DA function, activation of presynaptic D₂-like autoreceptors and the consequent reduction in DA neurotransmission may contribute to the beneficial effects of stimulants.

3.1.2. Norepinephrine

In addition to stimulants that potentiate NE as well as DA, other NE-potentiating agents including tricyclic antidepressants and more selective NE-uptake inhibitors (NRIs), as well as clonidine (a direct postsynaptic α_2 agonist in addition to its α_2 -autoreceptor effects that diminish NE-release) are all effective in treating ADHD [32,33,198]. These findings suggest that the central noradrenergic system may be involved in the disorder. Projecting widely throughout the CNS, NE neurons arising in their principal brainstem cell group, the locus coeruleus, are exquisitely sensitive to novelty, suggesting that they are involved in maintaining vigilance and directing attention to relevant stimuli [15,197]. Conversely, reduced central noradrenergic tone may impair these functions [33,197]. Consistent with this hypothesis, selective and extensive depletion of NE in neonatal rat, which can be achieved with 6-OHDA in the presence of a selective DAT-inhibitor [274], leads to motor hyperactivity [207], learning deficits [213], and distractibility in a rodent model that selectively assesses sustained attention [49]. Behavioral effects of drugs that potentiate NE transmission in laboratory models also are consistent with the effectiveness of such agents in the treatment of clinical ADHD.

Contrary to expectations of deficient NE neurotransmission in animal models of ADHD, analyses of the NE

Table 1
Comparison of animal models of ADHD

Model	Similarities to ADHD	Differences from ADHD	Comments
SHR	Hyperactivity in novel environment Motor impulsivity Attention deficit Some response to stimulants	Little association of hypertension with ADHD No sex differences in model Antihypertensives reduce model cognitive deficits and α_2 agonists benefit ADHD (direct central effect?)	Most thoroughly studied ADHD model Need more comparisons of pure hyperactive (WKHA) and hypertensive (WKHT) rats
DAT-KO mouse	Environment-dependent hyperactivity Stimulants reduce hyperactivity Cognitive impairment (radial maze)	Stimulant effects on cognition untested Methylphenidate requires high doses 5-HT agents beneficial in model, not in ADHD Evidence of DAT-excess in ADHD	No evidence of DA functional excess in ADHD
Coloboma neutron-irradiated mouse	Spontaneous hyperactivity Low-dose amphetamine reduces hyperactivity	Questionable relationship of ADHD to SNAP-25 gene Not improved by methylphenidate	Specific neural deficits not clear Cognition not well evaluated
NHE rat	Hyperactivity and attention deficits	Circadian motility normal	Requires neuropharmacological evaluation
Acallosal Mouse (I/LnJ)	Excessive arousal in novel environment Impulsive	Stimulants not tested No evidence of callosal dysfunction in ADHD	Needs further characterization
6-OHDA lesioned juvenile rat	Increased nonadaptive locomotor activity No sensory or motor deficits Stimulants attenuate hyperactivity and learning deficits	Lack of sex differences D_4 antagonists reduce hyperactivity	More assessment of attention and impulsivity needed D_4 antagonists need clinical testing
Neonatal anoxic rat	Some hyperactivity Deficits in learning and spatial memory Less active with amphetamine	Hyperactivity short-lived Cognitive effects of stimulants unknown Role of hypoxia in ADHD uncertain	Requires more pharmacological analysis
Cerebellar stunted rat	Hyperactive in novel environment Males more hyperactive	Attention and impulsivity not tested Stimulants untested Cerebellar dysfunction unproved in ADHD	Needs more behavioral comparisons to ADHD Role of cerebellum in ADHD requires assessment
Environmental toxins	Motor hyperactivity common in many species with varied toxins	Stimulant effects have limited testing Relationship of toxins to ADHD not proved	Mediating mechanisms not specified
Hippocampal X-irradiated rat	Hyperactivity present Deficits in memory-based learning Amphetamine improves learning	Stimulant effects on hyperactivity untested Radiation not implicated in ADHD	May model microneuronal hypoplasia or "minimum brain dysfunction"
Spontaneously inattentive rats	Deficits in sustained attention	Ethylphenidate not beneficial	Pathophysiology undefined
Hyposexual male rat	Spontaneous hyperactivity Deficits in attention Amphetamine reduces hyperactivity	Stimulants untested in ADHD ADHD also in females	ADHD sex-linked in hyperactivity, not to attentional deficits

Abbreviations: DA, dopamine; DAT-KO, dopamine transporter gene knock-out mouse; 5-HT, 5-hydroxytryptamine, serotonin; NHE rat, Naples high-excitability rat; 6-OHDA, 6-hydroxydopamine; SHR, spontaneously hypertensive rat; SNAP-25, synaptosomal associated protein of 25 kDa; WKY, Wistar-Kyoto rat; WKHA, Wistar-Kyoto rat, hyperactive not hypertensive; WKHT, Wistar-Kyoto rat, hypertensive not hyperactive.

system in most ADHD models have indicated normal or increased NE transmission, not decreases. Recent studies of NET-knockout mice also yield little support for a role of excessive NE in ADHD. These mutants did not show altered spontaneous activity or unusual responses to stimulants, although their motor responses to D_2 -agonist quinpirole and D_3/D_2 -agonist 7-hydroxydipropylamino-tetralin (7-OH-DPAT) were increased [300]. The striking

disparity between the pathophysiology of animal models of ADHD, and the beneficial effects of NE-potentiating agents in both animal models and in patients with ADHD, call for further consideration of the NE system in both modeling and treatment of ADHD.

3.1.3. Serotonin

Serotonergic neurons display distinctive slow, regular

discharges that change across the sleep–wake cycle and become virtually silent during rapid eye-movement (REM) sleep [132,133]. These neurons coordinate autonomic and neuroendocrine functions with changing motor output, and regulate sensory information processing, as well as exerting motor-facilitating effects at the lateral horn motoneurons [103]. When the 5-HT system is suppressed, such as with orientation to salient stimuli and in REM sleep, motor function is inhibited, and sensory information processing is activated [103,132,133].

Serotonin has been studied closely in few of the animal models of ADHD. In neonatally 6-OHDA lesioned rats, a role of 5-HT transmission is suggested by prominent hyperinnervation of neostriatum with 5-HT fibers and the inhibitory effects of 5-HT-potentiating agents on motor hyperactivity (see Section 2.2.1). In DAT-KO mice, 5-HT also may be critically involved in mediating the behavior-inhibiting effects of stimulants (see Section 2.1.2). Nevertheless, the relevance of these findings to clinical ADHD remains unclear, since fenfluramine and SRIs are not therapeutically effective in ADHD patients [26,198,233].

3.1.4. Acetylcholine and histamine

Maternal smoking is a risk factor for ADHD, and conversely, ADHD is a reported risk factor for early cigarette smoking in children [59,172–174], suggesting that central cholinergic system may be involved in ADHD. A role of cholinergic transmission in ADHD also is generally consistent with evidence of the critical importance of this neurotransmission system in cognitive functions (see Section 2.3.2), and specifically supported by clinical trials finding that treatment with both nicotine and the nicotinic agonist ABT-418 improved attention and arousal in ADHD subjects [62,291].

The central histaminergic system is also implicated in modifying attention and vigilance, possibly through modulating release of DA, NE, and 5-HT [192]. Of note, a new histamine H_3 -antagonist GT-2331 is being evaluated as a treatment for ADHD [1,273].

3.1.5. Actions of stimulant drugs

Extensively used to treat patients with ADHD for many years, stimulants such as amphetamine and methylphenidate provide important tests of the validity of animal models of the disorder [56,58,67,187,233]. These drugs are short-acting, with maximal plasma levels and therapeutic actions at 1–3 h, and plasma half-life of 4–8 h in man (much less in rodents) [43,56,58,155,167,169]. Effective daily oral doses for d-amphetamine in children with ADHD are 0.2–0.8 mg/kg, and for dl-methylphenidate, 0.3–1.0 mg/kg [56,58,249]. Methylphenidate can reduce motor hyperactivity in children with ADHD at a dose as low as 0.1 mg/kg, whereas high doses may lead to increased activity and compulsive or stereotyped behaviors and abnormal movements including tics [252,257]. Symptoms of ADHD return within hours after stimulants are

discontinued, and within prolonged dosing intervals [17,20,56,233].

There is no evidence of tolerance to clinical benefits of stimulants during prolonged daily use for years, perhaps reflecting their rapid clearance and typical use only during part of each day. However, there is evidence of tachyphylaxis to methylphenidate given in long-acting formulations, with rapidly evolving loss of clinical benefits within hours [107,267]. Clinical use of pulsed-release methylphenidate in rising doses may provide an advantage for children for whom mid-day dosing is a problem, since a single morning dose can afford beneficial behavioral effects throughout the day equivalent to standard twice-daily methylphenidate dosing, while also avoiding loss of response through rapidly evolving pharmacodynamic tolerance [176,177,193,196]. These pharmacological characteristics of stimulants need to be considered in evaluating proposed animal models of ADHD, as well as in optimizing the clinical therapeutics of the disorder.

Responses to stimulants in ADHD patients and normal human subjects vary widely and are not reliably predicted by age, body weight, or blood drug concentration [17,20]. These agents improve attention and reduce activity levels and impulsivity in ADHD patients as well as in normal subjects, probably through enhancing executive functions of the prefrontal cerebral cortex [17,20,204,205]. Based on brain-imaging studies, differences in behavioral responses to methylphenidate correlated with the amount of DA released, suggesting that with an equivalent level of DAT blockade, methylphenidate would produce less release of DA with lower levels of DA neuronal activity [270,284].

A fundamental paradox is that, at low doses, stimulants reduce hyperactivity in several ADHD animal models as well as in clinical ADHD, whereas high doses of same stimulants produce generalized stimulation of nervous system and increase motor activity. Several hypotheses have been offered to resolve this seeming inconsistency [235,236]. They include the idea that stimulants have biphasic effects. Low doses of stimulants reduce the extent to which DA is released with nerve impulses, possibly by activating autoreceptors. This effect reduces activation of postsynaptic D_1 and D_2 receptors, with reduced psychomotor activity [235,236]. At high doses, stimulants increase the release of DA with nerve impulses, elevate the concentrations of extracellular DA, and subsequently increase motor activity by activating postsynaptic $DA D_1$ and D_2 receptors, and overcoming presynaptic inhibition of DA release [235,236].

3.2. Implications for future studies of ADHD

Most of the experimental models of ADHD considered above rely on behavioral hyperactivity as a primary index to assess effects of clinically proven treatments for ADHD, such as stimulants and tricyclic antidepressants. Much less is known about the effects of these treatments on attention

and impulsivity in these models, though they can provide benefits for these features, as well as for hyperactivity, in clinical ADHD [20,290]. Animal modeling of ADHD is also limited by the still-evolving understanding of the clinical disorder. ADHD has traditionally been perceived as being four to six times more frequent among males than females. However, this view is biased by the prominence of hyperactive and dyssocial behaviors in boys and young men with ADHD [101]. Both brain-imaging studies [55] and psychological testing [237,238] suggest strong similarities between male and female ADHD patients.

There is a great need to bridge the gap between clinical and basic research relevant to ADHD. For example, more than 30 structural and functional neuroimaging studies of the brain in patients diagnosed with ADHD have been reported, using computerized tomography, magnetic resonance imaging, regional cerebral blood flow, glucose metabolism, and radioligand competition assays [104,184,206]. Most of these studies implicate the prefrontal cerebral cortex and its innervation of subcortical regions such as caudate-putamen, nucleus accumbens, and amygdaloid complex, in the pathophysiology of ADHD. Similarities between patients with ADHD and subjects with PFC lesions, especially in right hemisphere, also support the hypothesis that dysfunction of PFC is a critical component of ADHD [7,9,21,27,57,129,168,170,195,244,292,295]. Studies of the PFC in animal models remain rare, but those that are available, coupled with studies in human subjects, indicate that the right, dorsal PFC may be particularly important for sustaining attention and inhibiting responses to distracting stimuli [54,129,287,292], and that the right orbital PFC regulates behavioral and motor activity [9,265]. These systems should be considered in future studies of animal models of ADHD.

Despite the many advances in developing and analyzing animal models of ADHD, an ideal laboratory model for ADHD has yet to be established. Solanto proposed [254] that valid models of clinical ADHD should include: (a) deficits in measures of attention and impulsivity, and not only motor hyperactivity; (b) amelioration of both cognitive and motor deficits by stimulants and other clinically effective treatments in clinically plausible doses; (c) immediate onset of action and lack of tolerance or sensitization with repeated administration of drugs used to treat ADHD; and (d) effects of therapeutic agents on both DA and NE neurotransmission.

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References

- [1] S.M. Ali, C.E. Tedford, R. Gregory, M.K. Handley, S.L. Yates, W.W. Hirth, J.G. Phillips, Design, synthesis, and structure-activity relationships of acetylene-based histamine H_3 receptor antagonists, *J. Med. Chem.* 42 (1999) 903–909.
- [2] J. Altman, Morphological and behavioral markers of environmentally induced retardation of brain development: an animal model, *Environ. Health Perspect.* 74 (1987) 153–168.
- [3] J. Altman, R.L. Brunner, S.A. Bayer, The hippocampus and behavioral maturation, *Behav. Biol.* 8 (1973) 557–596.
- [4] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, American Psychiatric Association, Washington, DC, 1994.
- [5] T. Archer, W. Danysz, A. Fredriksson, G. Jonsson, J. Luthman, E. Sundstrom, A. Teiling, Neonatal 6-hydroxydopamine-induced dopamine depletions: motor activity and performance in maze learning, *Pharmacol. Biochem. Behav.* 31 (1988) 357–364.
- [6] L.E. Arnold, Sex differences in ADHD: Conference summary, *J. Abnorm. Child Psychol.* 24 (1996) 555–569.
- [7] A.F.T. Arnsten, Catecholamine regulation of the prefrontal cortex, *J. Psychopharmacol.* 11 (1997) 151–162.
- [8] A.F.T. Arnsten, Genetics of Childhood disorders: XVIII. ADHD, Part 2: Norepinephrine has a critical modulatory influence on prefrontal cortical function, *J. Am. Acad. Child Adolesc. Psychiatry* 39 (2000) 1201–1203.
- [9] A.F.T. Arnsten, Modulation of prefrontal cortical–striatal circuits: relevance to therapeutic treatments for Tourette syndrome and attention-deficit hyperactivity disorder, *Adv. Neurol.* 85 (2001) 333–341.
- [10] A.F.T. Arnsten, J.X. Cai, P.S. Goldman-Rakic, The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes, *J. Neurosci.* 8 (1988) 4287–4298.
- [11] A.F.T. Arnsten, P.S. Goldman-Rakic, Alpha-2 adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates, *Science* 230 (1985) 1273–1276.
- [12] A.F.T. Arnsten, J.C. Steere, R.D. Hunt, The contribution of alpha-sub-2 noradrenergic mechanisms to prefrontal cortical cognitive function: potential significance for attention-deficit hyperactivity disorder, *Arch. Gen. Psychiatry* 53 (1996) 448–455.
- [13] V. Asghari, S. Sanyal, S. Buchwaldt, A. Paterson, V. Jovanovic, H.H.M. Van Tol, Modulation of intracellular cyclic AMP levels by different human dopamine D_4 receptor variants, *J. Biochem.* 65 (1995) 1157–1165.
- [14] R. Aspidi, U.A. Gironi Carnevale, J.A. Sergeant, A.G. Sadile, Non-selective attention and nitric oxide in putative animal models of Attention-Deficit Hyperactivity Disorder, *Behav. Brain Res.* 95 (1998) 123–133.
- [15] G. Aston-Jones, M.T. Shipley, M. Ennis, J.T. Williams, V.A. Pierbone, Restricted afferent control of locus coeruleus neurons revealed by anatomical, physiological, and pharmacological studies, in: D.J. Heal, C.A. Marsden (Eds.), *The Pharmacology of Noradrenaline in the Central Nervous System*, Oxford Medical Publications, Oxford, 1990, pp. 187–247.
- [16] R.A. Avery, J.S. Franowicz, C. Studholme, C.H. van Dyck, A.F.T. Arnsten, The alpha-2A adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task, *Neuropsychopharmacology* 23 (2000) 240–249.

- [17] R.A. Barkley, A review of stimulant drug research with hyperactive children, *J. Child Psychol. Psychiatry* 18 (1977) 137–165.
- [18] R.A. Barkley, The ecological validity of laboratory and analogue assessment methods of ADHD symptoms, *J. Abnorm. Child Psychol.* 19 (1991) 149–178.
- [19] R.A. Barkley, Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD, *Psychol. Bull.* 121 (1997) 65–94.
- [20] R.A. Barkley, *Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*, Guilford Press, New York, 1998.
- [21] R.A. Barkley, G. Grodzinsky, G.J. DuPaul, Frontal lobe function in attention deficit disorder with and without hyperactivity: a review and research report, *J. Abnorm. Child Psychol.* 20 (1992) 163–188.
- [22] R.A. Barkley, D.G. Ullman, A comparison of objective measures of activity and distractibility in hyperactive and nonhyperactive children, *J. Abnorm. Child Psychol.* 3 (1975) 231–244.
- [23] C.L. Barr, Genetics of childhood disorders: XXII. ADHD, Part 6: The dopamine D₄ receptor gene, *J. Am. Acad. Child Adolesc. Psychiatry* 40 (2001) 118–122.
- [24] C.L. Barr, Y. Feng, K. Wigg, S. Bloom, W. Roberts, M. Malone, R. Schachar, R. Tannock, J.L. Kennedy, Identification of DNA variants in the SNAP-25 gene and linkage study of these polymorphisms and attention-deficit hyperactivity disorder, *Mol. Psychiatry* 5 (2000) 405–409.
- [25] C.L. Barr, K. Wigg, G. Zai, W. Roberts, M. Malone, R. Schachar, R. Tannock, J.L. Kennedy, Attention-deficit hyperactivity disorder and the adrenergic receptors alpha-1C and -2C, *Mol. Psychiatry* 6 (2001) 334–337.
- [26] L. Barrickman, R. Noyes, S. Kuperman, E. Schumacher, M. Verda, Treatment of ADHD with fluoxetine: a preliminary trial, *J. Am. Acad. Child Adolesc. Psychiatry* 30 (1991) 762–767.
- [27] R.T. Bartus, T.E. Levere, Frontal decortication in rhesus monkeys: a test of the interference hypothesis, *Brain Res.* 119 (1977) 233–248.
- [28] T.L. Baumgardner, H.S. Singer, M.B. Denckla, M.A. Rubin, M.T. Abrams, M.J. Colli, A.L. Reiss, Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder, *Neurology* 47 (1996) 477–482.
- [29] J. Benjamin, L. Li, C. Patterson, B.D. Greenberg, D.L. Murphy, D.H. Hamer, Population and familial association between D₄ dopamine receptor gene and measures of novelty-seeking, *Nat. Genet.* 12 (1996) 81–84.
- [30] D.F. Berger, T. Sagvolden, Sex differences in operant discrimination behaviour in an animal model of attention-deficit hyperactivity disorder, *Behav. Brain Res.* 94 (1998) 73–82.
- [31] P.C. Berquin, J.N. Giedd, L.K. Jacobsen, S.D. Hamburger, A.L. Krain, J.L. Rapoport, F.X. Castellanos, Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study, *Neurology* 50 (1998) 1087–1093.
- [32] J. Biederman, T. Spencer, Non-stimulant treatments for ADHD, *Eur. Child. Adolesc. Psychiatry* 9 (Suppl. 1) (2000) 151–159.
- [33] J. Biederman, T. Spencer, Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder, *Biol. Psychiatry* 46 (1999) 1234–1242.
- [34] V. Blanchard, M. Christin, S. Vyas, M. Savasta, C. Feuerstein, Y. Agid, F. Javoy-Agid, R. Raisman-Vozari, Long-term induction of tyrosine hydroxylase expression: compensatory response to partial degeneration of the dopaminergic nigrostriatal system in the rat brain, *J. Neurochem.* 64 (1995) 1669–1679.
- [35] G.J. Bloch, P.C. Butler, J.G. Kohlert, Galanin microinjected into the medial preoptic nucleus facilitates female- and male-typical sexual behaviors in the female rat, *Physiol. Behav.* 59 (1996) 1147–1154.
- [36] F. Boix, S.W. Qiao, T. Kolpus, T. Sagvolden, Chronic L-deprenyl treatment alters brain monoamine levels and reduces impulsiveness in an animal model of attention-deficit/hyperactivity disorder, *Behav. Brain Res.* 94 (1998) 153–162.
- [37] R. Bosse, F. Fumagalli, M. Jaber, B. Giros, R.R. Gainetdinov, W.C. Wetsel, C. Missale, M.G. Caron, Anterior pituitary hypoplasia and dwarfism in mice lacking the dopamine transporter, *Neuron* 19 (1997) 127–138.
- [38] J.D.D. Bradley, C.J. Golden, Biological contributions to the presentation and understanding of attention-deficit/hyperactivity disorder: a review, *Clin. Psychol. Rev.* 21 (2001) 907–929.
- [39] G.R. Breese, A.A. Baumeister, T.J. McCrown, S.G. Emrick, G.D. Frye, K. Crotty, R.A. Mueller, Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine, *J. Pharmacol. Exp. Ther.* 231 (1984) 343–354.
- [40] G.R. Breese, A.A. Baumeister, T.C. Napier, G.D. Frye, R.A. Mueller, Evidence that D₁ dopamine receptors contribute to the supersensitive behavioral responses induced by 1-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine, *J. Pharmacol. Exp. Ther.* 235 (1985) 287–295.
- [41] G.R. Breese, G.E. Duncan, T.C. Napier, S.C. Bondy, L.C. Iorio, R.A. Mueller, 6-Hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D₁- and D₂-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding, *J. Pharmacol. Exp. Ther.* 240 (1987) 167–176.
- [42] G.R. Breese, T.C. Napier, R.A. Mueller, Dopamine agonist-induced locomotor activity in rats treated with 6-hydroxydopamine at differing ages: functional supersensitivity of D₁ dopamine receptors in neonatally lesioned rats, *J. Pharmacol. Exp. Ther.* 234 (1985) 447–455.
- [43] G.L. Brown, R.D. Hunt, M.H. Ebert, W.E. Bunney, I.J. Kopin, Plasma levels of d-amphetamine in hyperactive children. Serial behavior and motor responses, *Psychopharmacology* 62 (1979) 133–140.
- [44] J.P. Bruno, D. Jackson, M.J. Zigmond, E.M. Stricker, Effect of dopamine-depleting brain lesions in rat pups: role of striatal serotonergic neurons in behavior, *Behav. Neurosci.* 101 (1987) 806–811.
- [45] B. Carboni, C. Spilewoy, C. Vacca, M. Nosten-Bertrand, B. Giros, G. di Chiara, Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene, *J. Neurosci.* 21 (2001) RC141–RC144.
- [46] R.K. Carder, D. Jackson, H.J. Morris, R.D. Lund, M.J. Zigmond, Dopamine released from mesencephalic transplants restores modulation of striatal acetylcholine release after neonatal 6-hydroxydopamine: an in vitro analysis, *Exp. Neurol.* 105 (1989) 251–259.
- [47] R.K. Carder, A.M. Snyder-Keller, R.D. Lund, Amphetamine- and stress-induced turning after nigral transplants in neonatally dopamine-depleted rats, *Brain Res.* 430 (1987) 315–318.
- [48] M.P. Carey, L.M. Diewald, F.J. Esposito, M.P. Pellicano, U.A.G. Carnevale, J.A. Sergeant, M. Papa, A.G. Sadile, Differential distribution, affinity and plasticity of dopamine D₁ and D₂ receptors in the target sites of the mesolimbic system in an animal model of ADHD, *Behav. Brain Res.* 94 (1998) 173–185.
- [49] M. Carli, T.W. Robbins, J.L. Evenden, B.J. Everitt, Effects of lesions to ascending noradrenergic neurons on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal, *Behav. Brain Res.* 9 (1983) 361–380.
- [50] E. Castaneda, I.Q. Whishaw, L. Lerner, T.E. Robinson, Dopamine depletion in neonatal rats: effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood, *Brain Res.* 508 (1990) 30–39.
- [51] F.X. Castellanos, Toward a pathophysiology of attention-deficit/hyperactivity disorder, *Clin. Pediatr.* 36 (1997) 381–393.
- [52] F.X. Castellanos, J. Elia, M.J. Kruesi, C.S. Gulotta, I.N. Mefford, W.Z. Potter, G.F. Ritchie, J.L. Rapoport, Cerebrospinal fluid monoamine metabolites in boys with attention-deficit hyperactivity disorder, *Psychiatry Res.* 52 (1994) 305–316.
- [53] F.X. Castellanos, J. Elia, M.J. Kruesi, W.L. Marsh, C.S. Gulotta,

- W.Z. Potter, G.F. Ritchie, S.D. Hamburger, J.L. Rapoport, Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit/hyperactivity disorder, *Neuropsychopharmacology* 14 (1996) 125–137.
- [54] F.X. Castellanos, J.N. Giedd, W.L. Marsh, S.D. Hamburger, A.C. Vaituzis, D.P. Dickstein, S.E. Sarfatti, Y.C. Vauss, J.W. Snell, N. Lange, D. Kaysen, A.L. Krain, G.F. Ritchie, J.C. Rajapakse, J.L. Rapoport, Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder, *Arch. Gen. Psychiatry* 53 (1996) 607–616.
- [55] F.X. Castellanos, J.N. Giedd, P.C. Berquin, J.M. Walter, W. Sharp, T. Tran, A.C. Vaituzis, J.D. Blumenthal, J. Nelson, T.M. Bastain, A. Zijdenbos, A.C. Evans, J.L. Rapoport, Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder, *Arch. Gen. Psychiatry* 58 (2001) 289–295.
- [56] T.D. Challman, J.J. Lipsky, Methylphenidate: Its pharmacology and uses, *Mayo Clin. Proc.* 75 (2000) 711–721.
- [57] L.L. Chao, R.T. Knight, Human prefrontal lesions increase distractibility to irrelevant sensory inputs, *Neuroreport* 21 (1995) 1605–1610.
- [58] B. Coffey, R.I. Shader, D.J. Greenblatt, Pharmacokinetics of benzodiazepines and psychostimulants in children, *J. Clin. Psychopharmacol.* 3 (1983) 217–225.
- [59] R.W. Cogger, K.L. Moe, E.A. Serafetinides, Attention deficit disorder in adults and nicotine dependence: psychobiological factors in resistance to recovery?, *J. Psychoactive Drugs* 28 (1996) 229–240.
- [60] B.J. Cole, T.W. Robbins, Forebrain norepinephrine: role in controlled information processing in the rat, *Neuropsychopharmacology* 7 (1992) 129–142.
- [61] B.J. Cole, T.W. Robbins, Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi on performance of a 5-choice serial reaction time task in rats: implications for theories of selective attention and arousal, *Beh. Brain Res.* 33 (1989) 165–179.
- [62] C.K. Connors, E.D. Levin, E. Sparrow, S.C. Hinton, D. Erhardt, W.H. Meek, J.E. Rose, J. March, Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD), *Psychopharmacol. Bull.* 32 (1996) 67–73.
- [63] E.H. Cook, M.A. Stein, M.D. Krasowski, N.J. Cox, D.M. Olkon, J.E. Kieffer, B.L. Leventhal, Association of attention-deficit disorder and the dopamine transporter gene, *Am. J. Hum. Genet.* 56 (1995) 993–998.
- [64] I. Creese, S.D. Iversen, Blockade of amphetamine-induced motor stimulation and stereotypy in the adult rat following neonatal treatment with 6-hydroxydopamine, *Brain Res.* 55 (1973) 369–382.
- [65] C.E. Cunningham, B.B. Benness, L.S. Siegel, Family functioning, time allocation, and parental depression in the families of normal and ADHD children, *J. Clin. Child Psychol.* 17 (1988) 169–177.
- [66] A. Czurko, B. Czeh, L. Seress, L. Nadel, J. Bures, Severe spatial navigation deficit in the Morris water maze after single high dose of neonatal X-ray irradiation in the rat, *Proc. Natl. Acad. Sci. USA* 94 (1997) 2766–2771.
- [67] E. Davids, K. Zhang, F.I. Tarazi, R.J. Baldessarini, Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning, *Psychopharmacology* 160 (2002) 92–98.
- [68] E. Davids, K. Zhang, N.S. Kula, F.I. Tarazi, R.J. Baldessarini, Effects of norepinephrine and serotonin transporter inhibitors on hyperactivity induced by neonatal 6-hydroxydopamine lesioning in rats, *J. Pharmacol. Exp. Ther.* 301 (2002) 1097–1102.
- [69] M.E. Dell'Anna, M.C. Geloso, G. Draisci, J. Luthman, Transient changes in FOS and GFAP immunoreactivity precede neuronal loss in the rat hippocampus following neonatal anoxia, *Exp. Neurol.* 131 (1995) 144–156.
- [70] M.E. Dell'Anna, J. Luthman, E. Lindqvist, L. Olson, Development of monoamine systems after neonatal anoxia in rats, *Brain Res. Bull.* 32 (1993) 159–170.
- [71] L. Descarries, J.J. Soghomonian, S. Garcia, G. Doucet, J.P. Bruno, Ultrastructural analysis of the serotonin hyperinnervation in adult rat neostriatum following neonatal dopamine denervation with 6-hydroxydopamine, *Brain Res.* 569 (1992) 1–13.
- [72] A.Y. Deutch, R.H. Roth, The determinants of stress-induced activation of the prefrontal cortical dopamine system, *Prog. Brain Res.* 85 (1990) 367–402.
- [73] J.L. Diaz-Granados, P.L. Greene, A. Amsel, Memory-based learning in preweanling and adult rats after infantile X-irradiation-induced hippocampal granule cell hypoplasia, *Behav. Neurosci.* 106 (1992) 940–946.
- [74] J.L. Diaz-Granados, P.L. Greene, A. Amsel, Selective activity enhancement and persistence in weanling rats after hippocampal X-irradiation in infancy: possible relevance for ADHD, *Behav. Neural. Biol.* 61 (1994) 251–259.
- [75] D.D. Dougherty, A.A. Bonab, T.J. Spencer, S.L. Rauch, B.K. Madras, A.J. Fischman, Dopamine transporter density in patients with attention deficit hyperactivity disorder, *Lancet* 354 (1999) 2132–2133.
- [76] S.H. Dresel, J. Krause, K.H. Krause, C. LaFougere, K. Brinkhauser, H.F. Kung, K. Hahn, K. Tatsch, Attention deficit hyperactivity disorder: binding of [^{99m}Tc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment, *Eur. J. Nucl. Med.* 27 (2000) 1518–1524.
- [77] R.P. Ebstein, O. Novik, R. Umansky, B. Priel, Y. Osher, D. Blaine, E.R. Bennett, L. Nemanov, M. Katz, R.H. Belmaker, Dopamine D₄ receptor (DRD4) exon III polymorphism associated with the human personality trait of novelty-seeking, *Nat. Genet.* 12 (1996) 78–80.
- [78] J. Eisenberg, A. Zohar, G. Mei-Tal, A. Steinberg, E. Tartakovsky, I. Gritsenko, L. Nemanov, R.P. Ebstein, A haplotype relative risk study of the dopamine D₄ receptor (DRD4) Exon III repeat polymorphism and attention deficit hyperactivity disorder (ADHD), *Am. J. Med. Genet.* 96 (2000) 258–261.
- [79] L. Erinoff, R.C. MacPhail, A. Heller, L.S. Seiden, Age-dependent effects of 6-hydroxydopamine on locomotor activity in the rat, *Brain Res.* 164 (1979) 195–205.
- [80] M. Ernst, R.M. Cohen, L.L. Liebenauer, P.H. Jones, A.J. Zametkin, Cerebral glucose metabolism in adolescent girls with attention-deficit/hyperactivity disorder, *J. Am. Acad. Child Adolesc. Psychiatry* 36 (1997) 1399–1406.
- [81] M. Ernst, L.L. Liebenauer, A.C. King, G.A. Fitzgerald, R.M. Cohen, A.J. Zametkin, Reduced brain metabolism in hyperactive girls, *J. Am. Acad. Child Adolesc. Psychiatry* 33 (1994) 858–868.
- [82] M. Ernst, A.J. Zametkin, J.A. Matochik, P.H. Jones, R.M. Cohen, DOPA decarboxylase activity in attention deficit hyperactivity disorder adults: A [¹⁸F]fluorodopa positron emission tomographic study, *J. Neurosci.* 18 (1998) 5901–5907.
- [83] M. Ernst, A.J. Zametkin, J.A. Matochik, D. Pascualvaca, P.H. Jones, R.M. Cohen, High midbrain [¹⁸F]DOPA accumulation in children with attention deficit hyperactivity disorder, *Am. J. Psychiatry* 156 (1999) 1209–1215.
- [84] C. Fahlke, S. Hansen, Alcohol responsiveness, hyperactivity, and motor restlessness in an animal model for attention-deficit hyperactivity disorder, *Psychopharmacology* 146 (1999) 1–9.
- [85] S.V. Faraone, J. Biederman, Neurobiology of attention-deficit hyperactivity disorder, *Biol. Psychiatry* 44 (1998) 951–958.
- [86] S.V. Faraone, J. Biederman, B. Weiffenbach, T. Keith, M.P. Chu, A. Weaver, T.J. Spencer, T.E. Wilens, J. Frazier, M. Cleves, J. Sakai, Dopamine D₄ gene 7-repeat allele and attention deficit hyperactivity disorder, *Am. J. Psychiatry* 156 (1999) 768–770.
- [87] S.V. Faraone, A.E. Doyle, E. Mick, J. Biederman, Meta-analysis of the association between the 7-repeat allele of the dopamine D₄ receptor gene and attention deficit hyperactivity disorder, *Am. J. Psychiatry* 158 (2001) 1052–1057.
- [88] S.A. Ferguson, Neuroanatomical and functional alterations resulting from early postnatal cerebellar insults in rodents, *Pharmacol. Biochem. Behav.* 55 (1996) 663–671.
- [89] S.A. Ferguson, A review of rodent models of ADHD, in: M.V.

- Solanto, A.F.T., Arnsten, F.X., Castellanos (Eds.), *Stimulant Drugs and ADHD*, Basic and Clinical Neuroscience, University Press, Oxford, 2001, pp. 209–220.
- [90] S.A. Ferguson, M.G. Paule, R.R. Holson, Functional effects of methylazoxymethanol-induced cerebellar hypoplasia in rats, *Neurotoxicol. Teratol.* 18 (1996) 529–537.
- [91] J.A. Fiez, Cerebellar contributions to cognition, *Neuron* 16 (1996) 13–15.
- [92] P.A. Filipek, M. Semrud-Clikeman, R.J. Steingard, P.F. Renshaw, D.N. Kennedy, J. Biederman, Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls, *Neurology* 48 (1997) 589–601.
- [93] A. Frazer, G.A. Gerhardt, L.C. Daws, New views of biogenic amine transporter function: implications for neuropsychopharmacology, *Int. J. Neuropsychopharmacol.* 2 (1999) 305–320.
- [94] P.A. Frohna, B.S. Neal-Beliveau, J.N. Joyce, Delayed plasticity of the mesolimbic dopamine system following neonatal 6-OHDA lesions, *Synapse* 25 (1997) 293–305.
- [95] S. Fuke, S. Suo, N. Takahashi, H. Koike, N. Sasagawa, S. Ishiura, The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression, *Pharmacogenomics* 1 (2001) 152–156.
- [96] F. Fumagalli, S. Jones, R. Bosse, M. Jaber, B. Giros, C. Missale, R.M. Wightman, M.G. Caron, Inactivation of the dopamine transporter reveals essential roles of dopamine in the control of locomotion, psychostimulant response, and pituitary function, *Adv. Pharmacol.* 42 (1998) 179–182.
- [97] R.R. Gainetdinov, M.G. Caron, Genetics of childhood disorders: XXIV. ADHD, Part 8: Hyperdopaminergic mice as an animal model of ADHD, *J. Am. Acad. Child. Adolesc. Psychiatry* 40 (2001) 380–382.
- [98] R.R. Gainetdinov, S.R. Jones, F. Fumagalli, R.M. Wightman, M.G. Caron, Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis, *Brain Res. Brain Res. Rev.* 26 (1998) 148–153.
- [99] R.R. Gainetdinov, W.C. Wetsel, S.R. Jones, E.D. Levin, M. Jaber, M.G. Caron, Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity, *Science* 283 (1999) 397–401.
- [100] C. Garcia-Sanchez, A. Estevez-Gonzalez, E. Suarez-Romero, C. Junque, Right hemisphere dysfunction in subjects with attention-deficit disorder with and without hyperactivity, *J. Child Neurol.* 12 (1997) 107–115.
- [101] M. Gaub, C.L. Carlson, Gender differences in ADHD: a meta-analysis and critical review, *J. Am. Acad. Child Adolesc. Psychiatry* 36 (1997) 1036–1045.
- [102] R.A. Gazzara, J. Altman, Early postnatal X-irradiation of the hippocampus and discrimination learning in adult rats, *J. Comp. Physiol. Psychol.* 95 (1981) 484–495.
- [103] S.C. Gerson, R.J. Baldessarini, Motor effects of serotonin in the central nervous system, *Life Sci.* 27 (1980) 1435–1451.
- [104] J.N. Giedd, J. Blumenthal, E. Molloy, F.X. Castellanos, Brain imaging of attention deficit/hyperactivity disorder, *Ann. N.Y. Acad. Sci.* 931 (2001) 33–49.
- [105] M. Gill, G. Daly, S. Heron, Z. Hawi, M. Fitzgerald, Confirmation of association between attention deficit hyperactivity disorder and a dopamine transporter polymorphism, *Mol. Psychiatry* 2 (1997) 311–313.
- [106] B. Giros, M. Jaber, S.R. Jones, R.M. Wightman, M.G. Caron, Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter, *Nature* 379 (1996) 606–612.
- [107] M.A. Gonzalez, H.S. Pentikis, N. Anderl, M.F. Benedict, H.H. DeCory, S.J. Dirksen, S.J. Hatch, Methylphenidate bioavailability from two extended-release formulations, *Int. J. Clin. Pharmacol. Ther.* 40 (2002) 175–184.
- [108] F. Gonzalez-Lima, A.G. Sadile, Network operations revealed by brain metabolic mapping in a genetic model of hyperactivity and attention deficit: the Naples high- and low-excitability rats, *Neurosci. Biobehav. Rev.* 24 (2000) 157–160.
- [109] T. Gramate, J. Schmidt, The effect of early postnatal hypoxia on the development of locomotor activity in rats, *Biomed. Biochim. Acta* 45 (1986) 523–529.
- [110] C.S. Hartsough, N.M. Lambert, Medical factors in hyperactive and normal children: prenatal, developmental, and health history findings, *Am. J. Orthopsychiatry* 55 (1985) 190–201.
- [111] Z. Hawi, M. McCarron, A. Kirley, G. Daly, M. Fitzgerald, M. Gill, M. No association of the dopamine DRD4 receptor (DRD4) gene polymorphism with attention deficit hyperactivity disorder (ADHD) in the Irish population, *Am. J. Med. Genet.* 96 (2000) 268–272.
- [112] T.G. Heffner, L.S. Seiden, Possible involvement of serotonergic neurons in the reduction of locomotor hyperactivity caused by amphetamine in neonatal rats depleted of brain dopamine, *Brain Res.* 244 (1982) 81–90.
- [113] A. Heinz, D. Goldman, D.W. Jones, R. Palmour, D. Hommer, J.G. Gorey, K.S. Lee, M. Linnoila, D.R. Weinberger, Genotype influences in vivo dopamine transporter availability in human striatum, *Neuropsychopharmacology* 22 (2000) 133–139.
- [114] E.D. Hendley, WKHA rats with genetic hyperactivity and hyperreactivity to stress: A review, *Neurosci. Biobehav. Rev.* 24 (2000) 41–44.
- [115] E.D. Hendley, X.M. Fan, Regional differences in brain norepinephrine and dopamine uptake kinetics in inbred rat strains with hypertension and/or hyperactivity, *Brain Res.* 586 (1992) 44–52.
- [116] E.D. Hendley, D.J. Wessel, J. van Houten, Inbreeding of Wistar-Kyoto rat strain with hyperactivity but without hypertension, *Behav. Neural. Biol.* 45 (1986) 1–16.
- [117] E.J. Hess, K.A. Collins, N.G. Copeland, N.A. Jenkins, M.C. Wilson, Deletion map of the coloboma (Cm) locus on mouse chromosome 2, *Genomics* 21 (1994) 257–261.
- [118] E.J. Hess, K.A. Collins, M.C. Wilson, Mouse model of hyperkinesis implicates SNAP-25 in behavioral regulation, *J. Neurosci.* 16 (1996) 3104–3111.
- [119] E.J. Hess, H.A. Finnah, C.A. Kozak, M.C. Wilson, Spontaneous locomotor hyperactivity in a mouse mutant with a deletion including the SNAP gene on chromosome 2, *J. Neurosci.* 12 (1992) 2865–2874.
- [120] E.J. Hess, P.K. Rogan, M. Domoto, D.E. Tinker, R.L. Ladda, J.C. Ramer, Absence of linkage of apparently single gene mediated ADHD with the human syntenic region of the mouse mutant Coloboma, *Am. J. Med. Genet.* 18 (1995) 573–579.
- [121] C.J. Heyser, M.C. Wilson, L.H. Gold, Coloboma hyperactive mutant exhibits delayed neurobehavioral developmental milestones, *Brain Res. Dev. Brain Res.* 89 (1995) 264–269.
- [122] D.A. Highfield, D. Hu, A. Amsel, Alleviation of X-irradiation-based deficit in memory-based learning by d-amphetamine: suggestions for attention deficit-hyperactivity disorder, *Proc. Natl. Acad. Sci. USA* 95 (1998) 5785–5788.
- [123] E. Holene, I. Nafstad, J.U. Skaare, A. Bernhoft, P. Engen, T. Sagvolden, Behavioral effects of pre- and postnatal exposure to individual polychlorinated biphenyl congeners in rats, *Environ. Toxicol. Chem.* 14 (1995) 967–976.
- [124] E. Holene, I. Nafstad, J.U. Skaare, T. Sagvolden, Behavioural hyperactivity in rats following postnatal exposure to sub-toxic doses of polychlorinated congeners 153 and 126, *Behav. Brain Res.* 94 (1998) 213–224.
- [125] R.L. Holloway, P.J. Anderson, R. Defendini, C. Harper, Sexual dimorphism of the human corpus callosum from three independent samples: relative size of the corpus callosum, *Am. J. Physiol. Anthropol.* 92 (1993) 481–498.
- [126] R.R. Holson, R.A. Gazzara, S.A. Ferguson, J. Adams, Behavioral effects of low-dose gestational day 11–13 retinoic acid exposure, *Neurotoxicol. Teratol.* 19 (1997) 355–362.
- [127] R.D. Hunt, A.F. Arnsten, M.D. Asbell, An open trial of guanfacine

- in the treatment of attention-deficit hyperactivity disorder, *J. Am. Acad. Child Adolesc. Psychiatry* 34 (1995) 50–54.
- [128] R.D. Hunt, R.B. Minderaa, D.J. Cohen, Clonidine benefits children with attention deficit disorder and hyperactivity: report of a double-blind placebo-cross-over therapeutic trial, *J. Am. Acad. Child Adolesc. Psychiatry* 24 (1985) 617–629.
- [129] G.W. Hynd, M. Semrud-Clikeman, A.R. Lorys, E.S. Novey, D. Eliopoulos, Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity, *Arch. Neurol.* 47 (1990) 919–926.
- [130] M. Jaber, B. Dumartin, C. Sagne, J.W. Haycock, C. Roubert, B. Giros, B. Bloch, M.G. Caron, Differential regulation of tyrosine hydroxylase in the basal ganglia of mice lacking the dopamine transporter, *Eur. J. Neurosci.* 11 (1999) 3499–3511.
- [131] M. Jaber, S.R. Jones, R. Bosse, B. Giros, M.G. Caron, Dramatic regulation of tyrosine hydroxylase in the basal ganglia of mice lacking the dopamine transporter (Abstract), *Soc. Neurosci. Abstr.* 22 (1996) 1576.
- [132] B.L. Jacobs, C.A. Fornal, Serotonin and motor activity, *Curr. Opin. Neurobiol.* 7 (1997) 820–825.
- [133] B.L. Jacobs, C.A. Fornal, Activity of serotonergic neurons in behaving animals, *Neuropsychopharmacology* 21 (Suppl. 1) (1999) 9–15.
- [134] L. Jancke, J.F. Staiger, G. Schlaug, Y. Huang, H. Steinmetz, The relationship between corpus callosum size and forebrain volume, *Cereb. Cortex* 7 (1997) 48–56.
- [135] M.D. Jones, M.E. Williams, E.J. Hess, Abnormal presynaptic catecholamine regulation in a hyperactive SNAP-25-deficient mouse mutant, *Pharmacol. Biochem. Behav.* 68 (2001) 669–676.
- [136] S.R. Jones, R.R. Gainetdinov, X.T. Hu, D.C. Cooper, R.M. Wightman, F.J. White, M.G. Caron, Loss of autoreceptor functions in mice lacking the dopamine transporter, *Neurosci.* 2 (1999) 649–655.
- [137] S.R. Jones, R.R. Gainetdinov, M. Jaber, B. Giros, R.M. Wightman, M.G. Caron, Profound neuronal plasticity in response to inactivation of the dopamine transporter, *Proc. Natl. Acad. Sci. USA* 95 (1998) 4029–4034.
- [138] S.R. Jones, R.R. Gainetdinov, R.M. Wightman, M.G. Caron, Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter, *J. Neurosci.* 18 (1998) 1979–1986.
- [139] S.R. Jones, P.A. Garriss, C.D. Kilts, R.M. Wightman, Comparison of dopamine uptake in the basolateral amygdaloid nucleus, caudate-putamen, and nucleus accumbens of the rat, *J. Neurochem.* 64 (1995) 2581–2589.
- [140] J.N. Joyce, P.A. Frohna, B.S. Neal-Beliveau, Functional and molecular differentiation of the dopamine system induced by neonatal denervation, *Neurosci. Biobehav. Rev.* 20 (1996) 453–486.
- [141] L. Kent, F. Middle, Z. Hawi, M. Fitzgerald, M. Gill, C. Feehan, N. Craddock, Nicotinic acetylcholine receptor alpha4 subunit gene polymorphism and attention deficit hyperactivity disorder, *Psychiatr. Genet.* 11 (2001) 37–40.
- [142] J.G. Kohlert, G.J. Bloch, A rat model for attention deficit-hyperactivity disorder, *Physiol. Behav.* 53 (1993) 1215–1218.
- [143] J.G. Kohlert, G.J. Bloch, Hyperactivity in hyposexual male rats, *Physiol. Behav.* 59 (1996) 171–178.
- [144] B. Applegate, B.B. Lahey, E.L. Hart, J. Biederman, G.W. Hynd, R.A. Barkley, T. Ollendick, P.J. Frick, L. Greenhill, K. McBurnett, J.H. Newcorn, L. Kerdyk, B. Garfinkel, I. Waldman, D. Shaffer, Validity of the age-of-onset criterion for ADHD: a report from the DSM-IV field trials, *J. Am. Acad. Child. Adolesc. Psychiatry* 36 (1997) 1211–1221.
- [145] R.M. Kostzewska, T.A. Reader, L. Descarries, Serotonin neural adaptations to ontogenic loss of dopamine neurons in the rat brain, *J. Neurochem.* 70 (1998) 889–898.
- [146] K.H. Krause, S.H. Dresel, J. Krause, H.F. Kung, K. Tatsch, Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography, *Neurosci. Lett.* 285 (2000) 107–110.
- [147] R. Kuczenski, D.S. Segal, Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine, *J. Neurochem.* 68 (1997) 2032–2037.
- [148] R. Kuczenski, D.S. Segal, Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine, *J. Pharmacol. Exp. Ther.* 296 (2001) 876–883.
- [149] N.S. Kula, R.J. Baldessarini, F.I. Tarazi, R. Fisser, S. Wang, J. Trometer, J.L. Neumeyer, [³H]β-CIT: A radioligand for dopamine transporters in rat brain tissue, *Eur. J. Pharmacol.* 385 (1999) 291–294.
- [150] B.B. Lahey, B. Applegate, K. McBurnett, J. Biederman, L. Greenhill, G.W. Hynd, R.A. Barkley, J. Newcorn, P. Jensen, J. Richters, B. Garfinkel, L. Kerdyk, P.J. Frick, T. Ollendick, D. Perez, E.L. Hart, I. Waldman, D. Shaffer, DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents, *Am. J. Psychiatry* 151 (1994) 1673–1685.
- [151] G.J. LaHoste, J.M. Swanson, S.B. Wigal, C. Glabe, T. Wigal, N. King, J.L. Kennedy, Dopamine D₄ receptor gene polymorphism is associated with attention deficit hyperactivity disorder, *Mol. Psychiatry* 1 (1996) 121–124.
- [152] H.C. Leiner, A.L. Leiner, R.S. Dow, Cognitive and language functions of the human cerebellum, *Trends Neurosci.* 16 (1993) 444–447.
- [153] E.D. Levin, C.K. Connors, E. Sparrow, S.C. Hinton, D. Erhardt, W.H. Meck, J.E. Rose, J. March, Nicotine effects on adults with attention-deficit/hyperactivity disorder, *Psychopharmacology* 123 (1996) 55–63.
- [154] E.D. Levin, S.L. Schantz, R.E. Bowman, Use of the lesion model for examining toxicant effects on cognitive behavior, *Neurotoxicol. Teratol.* 14 (1992) 131–141.
- [155] T. Lewander, On the presence of *p*-hydroxynorephedrine in the rat brain and heart in relation to changes in catecholamine levels after administration of amphetamine, *Acta Pharmacol. Toxicol.* 29 (1971) 3–48.
- [156] H.P. Lipp, R. Waanders, D.P. Wolfer, A new mouse model of partial and complete agenesis of the corpus callosum (Abstract), *Soc. Neurosci. Abstr.* 16 (1990) 925.
- [157] H.P. Lipp, D. Wahlsten, Absence of the corpus callosum, in: P. Driscoll (Ed.), *Genetically Defined Animal Models of Neurobehavioral Dysfunctions*, Birkhäuser, Boston, 1992, pp. 217–252.
- [158] J.W. Lomasney, W. Lorenz, L.F. Allen, K. King, J.W. Regan, T.L. Yang-Feng, M.G. Caron, R.J. Lefkowitz, Expansion of the alpha 2-adrenergic receptor family: cloning and characterization of a human alpha 2-adrenergic receptor subtype, the gene for which is located on chromosome 2, *Proc. Natl. Acad. Sci. USA* 87 (1990) 5094–5098.
- [159] H.C. Lou, Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy, *Acta Paediatr.* 85 (1996) 1266–1271.
- [160] J. Luthman, M. Bassen, A. Fredriksson, T. Archer, Functional changes induced by neonatal cerebral 6-hydroxydopamine treatment: effects of dose levels on behavioral parameters, *Behav. Brain Res.* 82 (1997) 213–221.
- [161] J. Luthman, E. Brodin, E. Sundstrom, B. Wiehager, Studies on brain monoamine and neuropeptide systems after neonatal intracerebroventricular 6-hydroxydopamine treatment, *Int. J. Dev. Neurosci.* 8 (1990) 549–560.
- [162] J. Luthman, A. Fredriksson, T. Lewander, G. Jonsson, T. Archer, Effects of d-amphetamine and methylphenidate on hyperactivity produced by neonatal 6-hydroxydopamine treatment, *Psychopharmacology* 99 (1989) 550–557.
- [163] I.K. Lyoo, G.G. Noam, C.K. Lee, H.K. Lee, B.P. Kennedy, P.F.

- Renshaw, The corpus callosum and lateral ventricles in children with attention-deficit hyperactivity disorder: a brain magnetic resonance imaging study, *Biol. Psychiatry* 40 (1996) 1060–1063.
- [164] B.K. Madras, G.M. Miller, A.J. Fischman, The dopamine transporter: relevance to attention deficit hyperactivity disorder (ADHD), *Behav. Brain Res.* 130 (2002) 57–63.
- [165] F. Magara, L. Ricceri, D.P. Wolfer, H.P. Lipp, The acallosal mouse strain I/LnJ: a putative model of ADHD?, *Neurosci. Biobehav. Rev.* 24 (2000) 45–50.
- [166] J.F. Marshall, J.S. Richardson, P. Teitelbaum, Nigrostriatal bundle damage and the lateral hypothalamic syndrome, *J. Comp. Physiol.* 87 (1974) 808–830.
- [167] S.B. Matin, S.H. Wan, J.B. Knight, Quantitative determination of enantiomeric compounds. Simultaneous measurement of the optical isomers of amphetamine in human plasma and saliva using chemical ionization mass spectrometry, *Biomed. Mass Spectr.* 4 (1977) 118–121.
- [168] J.A. Mattes, The role of frontal lobe dysfunction in childhood hyperkinesia, *Compr. Psychiatry* 21 (1980) 358–369.
- [169] W.P. Melega, A.E. Williams, D.A. Schmitz, E.W. DiStefano, A.K. Cho, Pharmacokinetic and pharmacodynamic analysis of the actions of d-amphetamine and d-methamphetamine on the dopamine terminal, *J. Pharmacol. Exp. Ther.* 274 (1995) 90–96.
- [170] M.M. Mesulam, A cortical network for directed attention and unilateral neglect, *Ann. Neurol.* 10 (1981) 309–325.
- [171] S.K. Michelhaugh, C. Fiskerstrand, E. Lovejoy, M.J. Bannon, J.P. Quinn, The dopamine transporter gene (SLC6A3) variable number of tandem repeats domain enhances transcription in dopamine neurons, *J. Neurochem.* 79 (2001) 1033–1038.
- [172] S. Mihailescu, R. Drucker-Colin, Nicotine, brain nicotinic receptors, and neuropsychiatric disorders, *Arch. Med. Res.* 31 (2000) 131–144.
- [173] S. Milberger, J. Biederman, S.V. Faraone, L. Chen, J. Jones, Further evidence of an association between attention-deficit/hyperactivity disorder and cigarette smoking. Findings from a high-risk sample of siblings, *Am. J. Addiction* 6 (1997) 205–217.
- [174] S. Milberger, J. Biederman, S.V. Faraone, L. Chen, J. Jones, ADHD is associated with early initiation of cigarette smoking in children and adolescents, *J. Am. Acad. Child Adolesc. Psychiatry* 36 (1997) 37–44.
- [175] G.M. Miller, B.K. Madras, Polymorphisms in the 3'-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression, *Mol. Psychiatry* 7 (2002) 44–55.
- [176] N.B. Modi, B. Wang, R.J. Noveck, S.K. Gupta, Dose-proportional and stereospecific pharmacokinetics of methylphenidate delivered using an osmotic, controlled-release oral delivery system, *J. Clin. Pharmacol.* 40 (2000) 1141–1149.
- [177] N.B. Modi, B. Lindemulder, S.K. Gupta, Single- and multiple-dose pharmacokinetics of an oral once-a-day osmotic controlled-release OROS (methylphenidate HCl) formulation, *J. Clin. Pharmacol.* 40 (2000) 379–388.
- [178] D.M. Mook, J. Jeffrey, A. Neuringer, Spontaneously hypertensive rats (SHR) readily learn to vary but not repeat instrumental responses, *Behav. Neural. Biol.* 59 (1993) 126–135.
- [179] M.B. Moser, E.L. Moser, B. Wultz, T. Sagvolden, Component analyses differentiate between exploratory behaviour of spontaneously hypertensive rats and Wistar Kyoto rats in a two-compartment free-exploration open field, *Scand. J. Psychol.* 29 (1988) 200–206.
- [180] J.L. Muir, B.J. Everitt, T.W. Robbins, AMPA-induced excitotoxic lesions of the basal forebrain: a significant role for the cortical cholinergic system in attentional function, *J. Neurosci.* 14 (1994) 2313–2326.
- [181] J.L. Muir, K.J. Page, D.J. Sirinathsinghi, T.W. Robbins, B.J. Everitt, Excitotoxic lesions of basal forebrain cholinergic neurons: effects on learning, memory and attention, *Behav. Brain Res.* 57 (1993) 123–131.
- [182] M.M. Myers, R.E. Musty, E.D. Hendley, Attenuation of hyperactivity in the spontaneously hypertensive rat by amphetamine, *Behav. Neural. Biol.* 34 (1982) 42–54.
- [183] M.M. Myers, S.R. Whitemore, E.D. Hendley, Changes in catecholamine neuronal uptake and receptor binding in the brains of spontaneously hypertensive rats (SHR), *Brain Res.* 220 (1981) 325–338.
- [184] H.A. Nasrallah, J. Loney, S.C. Olson, M. McCalley-Whiters, J. Kramer, C.G. Jacoby, Cortical atrophy in young adults with a history of hyperactivity in childhood, *Psychiatry Res.* 17 (1986) 241–246.
- [185] H.L. Needleman, The neurobehavioral consequences of low lead exposure in childhood, *Neurobehav. Toxicol. Teratol.* 4 (1982) 729–732.
- [186] H.L. Needleman, C. Ginnoc, A. Leviton, R. Reed, H. Peresie, C. Maher, P. Barrett, Deficits in psychologic and classroom performance of children with elevated dentine lead levels, *N. Engl. J. Med.* 300 (1979) 689–695.
- [187] E.J. Nestler, G.K. Aghajanian, Molecular and cellular basis of addiction, *Science* 278 (1997) 58–63.
- [188] K. Okamoto, K. Aoki, Development of a strain of spontaneously hypertensive rats, *Jpn. Circulation J.* 27 (1963) 282–293.
- [189] G.A. Ordway, Effect of noradrenergic lesions on subtypes of alpha-2 adrenoceptors in rat brain, *J. Neurochem.* 64 (1995) 1118–1126.
- [190] M. Papa, M.P. Pellicano, A. Cerbone, C. Lamberti-D'Mello, T. Memma, C. Buono, A. Giuditta, H. Welzl, A.G. Sadile, Immediate early genes and brain DNA remodeling in the Naples high- and low-excitability rat lines following exposure to a spatial novelty, *Brain Res. Bull.* 37 (1995) 111–118.
- [191] M. Papa, S. Sellitti, A.G. Sadile, Remodeling of neural networks in the anterior forebrain of an animal model of hyperactivity and attention deficits as monitored by molecular imaging probes, *Neurosci. Biobehav. Rev.* 24 (2000) 149–156.
- [192] M.B. Passani, L. Bacciottini, P.F. Mannaioni, P. Blandina, Central histaminergic system and cognition, *Neurosci. Biobehav. Rev.* 24 (2000) 107–113.
- [193] M.G. Paule, A.S. Rowland, S.A. Ferguson, J.J. Chelonis, R. Tannock, J.M. Swanson, F.X. Castellanos, Attention deficit/hyperactivity disorder: characteristics, interventions, and models, *Neurotoxicol. Teratol.* 22 (2000) 631–651.
- [194] D.L. Pauls, Genetic factors in the expression of attention-deficit hyperactivity disorder, *J. Child Adolesc. Psychopharmacol.* 1 (1991) 353–360.
- [195] G.D. Pearlson, R.G. Robinson, Suction lesions of the frontal cerebral cortex in the rat induce asymmetrical behavioral and catecholaminergic responses, *Brain Res.* 218 (1981) 233–242.
- [196] W.E. Pelham, E.M. Gnagy, A.M. Chronis, L. Burrows-MacLean, G.A. Fabiano, A.N. Onyango, D.L. Meichenbaum, A. Williams, H.R. Aronoff, R.L. Steiner, A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder, *Pediatrics* 104 (1999) 1300–1311.
- [197] S.R. Pliszka, J.T. McCracken, J.W. Maas, Catecholamines in attention-deficit hyperactivity disorder: current perspectives, *J. Am. Acad. Child Adolesc. Psychiatry* 35 (1996) 264–272.
- [198] C.W. Popper, Pharmacologic alternatives to psychostimulants for the treatment of attention-deficit/hyperactivity disorder, *Child Adolesc. Psychiatr. Clin. North Am.* 9 (2000) 605–646.
- [199] T. Puumala, M. Björklund, S. Ruotsalainen, M. Riekkinen, P. Jätkälä, A. Haapalio, E. Björk, P. Riekkinen, J. Sirviö, Lack of relationship between thalamic oscillations and attention in rats: Differential modulation by an alpha-2 antagonist, *Brain Res. Bull.* 43 (1997) 163–171.
- [200] T. Puumala, P. Riekkinen, J. Sirviö, Modulation of vigilance and behavioral activation by alpha-1 adrenoceptors in the rat, *Pharmacol. Biochem. Behav.* 56 (1997) 705–712.

- [201] T. Puumala, S. Ruotsalainen, P. Jäkälä, E. Koivisto, P. Riekkinen, J. Sirviö, Behavioral and pharmacological studies on the validation of a new animal model for attention deficit hyperactivity disorder, *Neurobiol. Learn. Memory* 66 (1996) 198–211.
- [202] T. Puumala, J. Sirviö, Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task, *Neuroscience* 83 (1997) 489–499.
- [203] J. Raber, P.P. Mehta, M. Kreifeldt, L.H. Parsons, F. Weiss, F.E. Bloom, M.C. Wilson, Coloboma hyperactive mutant mice exhibit regional and transmitter-specific deficits in neurotransmission, *J. Neurochem.* 68 (1997) 176–186.
- [204] J.L. Rapoport, M.S. Buchsbaum, H. Weingartner, T.P. Zahn, C. Ludlow, E.J. Mikkelsen, Dextroamphetamine. Its cognitive and behavioral effects in normal and hyperactive boys and normal men, *Arch. Gen. Psychiatry* 37 (1980) 933–943.
- [205] J.L. Rapoport, M.S. Buchsbaum, T.P. Zahn, H. Weingartner, C. Ludlow, E.J. Mikkelsen, Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys, *Science* 199 (1978) 560–563.
- [206] J.L. Rapoport, F.X. Castellanos, N. Gogate, K. Janson, S. Kohler, P. Nelson, Imaging normal and abnormal brain development: new perspectives for child psychiatry, *Aus. NZ J. Psychiatry* 35 (2001) 272–281.
- [207] L.A. Raskin, B.A. Shaywitz, G.M. Anderson, D.J. Cohen, M.H. Teicher, J. Linakis, Differential effects of selective dopamine, norepinephrine or catecholamine depletion on activity and learning in the developing rat, *Pharmacol. Biochem. Behav.* 19 (1983) 743–749.
- [208] T.A. Reader, K.M. Dewar, Effects of denervation and hyperinnervation on dopamine and serotonin systems in the rat neostriatum: implications for human Parkinsons disease, *Neurochem. Int.* 34 (1999) 1–21.
- [209] D.C. Rice, Anatomical substrates of behavioral impairment induced by developmental lead exposure in monkeys: inferences from brain lesions, *Am. Zool.* 37 (1997) 409–425.
- [210] D.C. Rice, Effect of postnatal exposure to a PCB mixture in monkeys on multiple fixed interval-fixed ratio performance, *Neurotoxicol. Teratol.* 19 (1997) 429–434.
- [211] D.C. Rice, Parallels between attention deficit hyperactivity disorder and behavioral deficits produced by neurotoxic exposure in monkeys, *Environ. Health Perspect.* 108 (2000) 405–408.
- [212] D.C. Rice, S. Hayward, Effects of postnatal exposure to a PCB mixture in monkeys on nonspatial discrimination reversal and delayed alternation performance, *Neurotoxicology* 18 (1997) 479–494.
- [213] D.C. Roberts, M.T. Price, H.C. Fibiger, The dorsal tegmental noradrenergic projection: an analysis of its role in maze learning, *J. Comp. Physiol. Psychol.* 90 (1976) 363–372.
- [214] T. Roman, M. Schmitz, G. Polanczyk, M. Eizirik, L.A. Rohde, M.H. Hutz, Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D₄ receptor gene, *Am. J. Med. Genet.* 105 (2001) 471–478.
- [215] R.B. Rothman, M.H. Baumann, C.M. Dersch, D.V. Romero, K.C. Rice, P.I. Carroll, J.S. Partilla, Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin, *Synapse* 39 (2001) 32–41.
- [216] D.K. Routh, R.D. Roberts, Minimal brain dysfunction in children: failure to find evidence for a behavioral syndrome, *Psychol. Rep.* 31 (1972) 307–314.
- [217] V.A. Russell, The nucleus accumbens motor-limbic interface of the spontaneously hypertensive rat as studied in vitro by the superfusion slice technique, *Neurosci. Biobehav. Rev.* 24 (2000) 133–136.
- [218] V.A. Russell, S. Allie, T. Wiggins, Increased noradrenergic activity in prefrontal cortex slices of an animal model for attention-deficit hyperactivity disorder—the spontaneously hypertensive rat, *Behav. Brain Res.* 117 (2000) 69–74.
- [219] V.A. Russell, A.S. de Villiers, T. Sagvolden, M.C. Lamm, J. Taljaard, Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention-deficit hyperactivity disorder—the spontaneously hypertensive rat, *Brain Res.* 676 (1995) 343–351.
- [220] V.A. Russell, A.S. de Villiers, T. Sagvolden, M.C. Lamm, J. Taljaard, Differences between electrically-, methylphenidate, and D-amphetamine-stimulated release of [³H]dopamine from brain slices suggest impaired vesicular storage of dopamine in an animal model of attention deficit-hyperactivity disorder, *Behav. Brain Res.* 94 (1998) 163–171.
- [221] V.A. Russell, A.S. de Villiers, T. Sagvolden, M.C. Lamm, J.J. Taljaard, Methylphenidate affects striatal differently in an animal model for attention-deficit/hyperactivity disorder—the spontaneously hypertensive rat, *Brain Res. Bull.* 53 (2000) 187–192.
- [222] V.A. Russell, T.M. Wiggins, Increased glutamate-stimulated norepinephrine release from prefrontal cortex slices of spontaneously hypertensive rats, *Metab. Brain Disord.* 15 (2000) 297–304.
- [223] A.G. Sadile, Multiple evidence of a segmental defect in the anterior forebrain of an animal model of hyperactivity and attention deficit, *Neurosci. Biobehav. Rev.* 24 (2000) 161–169.
- [224] A.G. Sadile, C. Lamberti, B. Siegfried, H. Welzl, Circadian activity, nociceptive thresholds, nigrostriatal and mesolimbic dopaminergic activity in the Naples high- and low-excitability rat lines, *Behav. Brain Res.* 55 (1993) 17–27.
- [225] A.G. Sadile, M.P. Pellicano, T. Sagvolden, J.A. Sergeant, NMDA and non-NMDA sensitive L-[³H]glutamate receptor binding in the brain of the Naples high- and low-excitability rats: an autoradiographic study, *Behav. Brain Res.* 78 (1996) 163–174.
- [226] S.H. Safe, Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment, *Crit. Rev. Toxicol.* 24 (1994) 87–149.
- [227] T. Sagvolden, Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD), *Neurosci. Biobehav. Rev.* 24 (2000) 31–39.
- [228] T. Sagvolden, H. Aase, P. Zeiner, D. Berger, Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder, *Behav. Brain Res.* 94 (1998) 61–71.
- [229] T. Sagvolden, M.A. Metzger, H.K. Schiorbeck, A.L. Rugland, I. Spinnangr, G. Sagvolden, The spontaneously hypertensive rat (SHR) as an animal model of childhood hyperactivity (ADHD): changed reactivity to reinforcers and to psychomotor stimulants, *Behav. Neural Biol.* 58 (1992) 103–112.
- [230] J.H. Satterfield, M.E. Dawson, Electrodermal correlates of hyperactivity in children, *Psychophysiology* (1971) 191–197.
- [231] L. Scabill, P.B. Chappell, Y.S. Kim, R.T. Schultz, L. Katsoch, E. Shepherd, A.F. Amsten, D.J. Cohen, J.F. Leckman, A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder, *Am. J. Psychiatry* 158 (2001) 1067–1074.
- [232] R.K.W. Schwarting, J.P. Huston, The unilateral 6-hydroxydopamine lesion model in behavioral brain research. Analysis of functional deficits, recovery and treatments, *Prog. Neurobiol.* 50 (1996) 275–331.
- [233] J.B. Schweitzer, T.K. Cummins, C.A. Kant, Attention-deficit/hyperactivity disorder, *Med. Clin. North Am.* 85 (2001) 757–777.
- [234] A.J. Searle, New mutants, Vol. 2: Coloboma, *Mouse Newslett.* 35 (1966) 27.
- [235] P. Seeman, B.K. Madras, Anti-hyperactivity medication: methylphenidate and amphetamine, *Mol. Psychiatry* 3 (1998) 386–396.
- [236] P. Seeman, B.K. Madras, Methylphenidate elevates resting dopamine which lowers the impulse-triggered release of dopamine: A hypothesis, *Behav. Brain Res.* 130 (2002) 79–83.
- [237] L.J. Seidman, J. Biederman, S.V. Faraone, W. Weber, D. Mennin, J. Jones, A pilot study of neuropsychological function in girls with ADHD, *J. Am. Acad. Child Adolesc. Psychiatry* 36 (1997) 366–373.

- [238] L.J. Seidman, J. Biederman, M.C. Monuteaux, A.E. Doyle, S.V. Faraone, Learning disabilities and executive dysfunction in boys with attention-deficit/hyperactivity disorder, *Neuropsychology* 15 (2001) 544–556.
- [239] D. Shaffer, L. Greenhill, A critical note on the predictive validity of 'the hyperkinetic syndrome', *J. Child Psychol. Psychiatry* 20 (1979) 61–72.
- [240] W. Shain, B. Bush, R. Seegal, Neurotoxicity of polychlorinated biphenyls: structure–activity relationship of individual congeners, *Toxicol. Appl. Pharmacol.* 111 (1991) 33–42.
- [241] B.A. Shaywitz, J.H. Klopfer, J.W. Gordon, Methylphenidate in 6-hydroxydopamine-treated developing rat pups. Effects on activity and maze performance, *Arch. Neurol.* 35 (1978) 463–469.
- [242] B.A. Shaywitz, J.H. Klopfer, R.D. Yager, J.W. Gordon, Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine, *Nature* 261 (1976) 153–155.
- [243] B.A. Shaywitz, R.D. Yager, J.H. Klopfer, Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction, *Science* 191 (1976) 305–308.
- [244] K.L. Shue, V.I. Douglas, Attention deficit hyperactivity disorder and the frontal syndrome, *Brain Cognit.* 20 (1992) 104–124.
- [245] E.K. Silbergeld, A.M. Goldberg, Lead-induced behavioral dysfunction: an animal model of hyperactivity, *Exp. Neurol.* 42 (1974) 146–157.
- [246] E.K. Silbergeld, A.M. Goldberg, Pharmacological and neurochemical investigations of lead-induced hyperactivity, *Neuropharmacology* 14 (1975) 431–444.
- [247] S.L. Smalley, J.N. Bailey, C.G. Palmer, D.P. Cantwell, J.J. McGough, M.A. Del'Homme, J.R. Asarnow, J.A. Woodward, C. Ramsey, S.F. Nelson, Evidence that the dopamine D₂ receptor is a susceptibility gene in attention deficit hyperactivity disorder, *Mol. Psychiatry* 3 (1998) 427–430.
- [248] R.D. Smith, B.R. Cooper, G.R. Breese, Growth and behavioral changes in developing rats treated intracisternally with 6-hydroxydopamine: evidence for involvement of brain dopamine, *J. Pharmacol. Exp. Ther.* 185 (1973) 609–619.
- [249] B.H. Smith, W.E. Pelham, E. Gnagy, R.S. Yudell, Equivalent effects of stimulant treatment for attention-deficit hyperactivity disorder during childhood and adolescence, *J. Am. Acad. Child Adolesc. Psychiatry* 37 (1998) 314–321.
- [250] A.M. Snyder-Keller, R.K. Carder, R.D. Lund, Development of dopamine innervation and turning behavior in dopamine-depleted infant rats receiving unilateral nigral transplants, *Neuroscience* 30 (1989) 779–794.
- [251] M.V. Solanto, Neuropharmacological basis of stimulant drug action in attention deficit disorder with hyperactivity: a review and synthesis, *Psychol. Bull.* 95 (1984) 387–409.
- [252] M.V. Solanto, Behavioral effects of low-dose methylphenidate in childhood attention deficit disorder: implications for a mechanism of stimulant drug action, *J. Am. Acad. Child Adolesc. Psychiatry* 25 (1986) 96–101.
- [253] M.V. Solanto, Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration, *Behav. Brain Res.* 94 (1998) 127–152.
- [254] M.V. Solanto, Clinical psychopharmacology of AD/HD: Implications for animal models, *Neurosci. Biobehav. Rev.* 24 (2000) 27–30.
- [255] Z. Speiser, J. Amitzi-Sonder, S. Gitter, S. Cohen, Behavioral differences in the developing rat following postnatal anoxia or postnatally injected AP-64A, a cholinergic neurotoxin, *Behav. Brain Res.* 30 (1988) 89–94.
- [256] Z. Speiser, A.D. Korczyn, I. Teplitzky, S. Gitter, Hyperactivity in rats following postnatal anoxia, *Behav. Brain Res.* 7 (1983) 379–382.
- [257] T. Spencer, J. Biederman, B. Coffey, D. Geller, M. Crawford, S.K. Bearman, R. Tarazi, S.V. Faraone, A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder, *Arch. Gen. Psychiatry* 59 (2002) 649–656.
- [258] C. Spielow, C. Roubert, M. Hamon, M. Nosten-Bertrand, C. Betancur, B. Giros, Behavioral disturbances associated with hyperdopaminergia in dopamine-transporter knockout mice, *Behav. Pharmacol.* 11 (2000) 279–290.
- [259] S. Sprich-Buckminster, J. Biederman, S. Milberger, S.V. Faraone, B.K. Lehman, Are perinatal complications relevant to the manifestation of ADD? Issues of comorbidity and familiarity, *J. Am. Acad. Child. Adolesc. Psychiatry* 32 (1993) 1032–1037.
- [260] M.K. Stachowiak, J.P. Bruno, A.M. Snyder, E.M. Stricker, M.J. Zigmond, Apparent sprouting of striatal serotonergic terminals after dopamine-depleting brain lesions in neonatal rats, *Brain Res.* 291 (1984) 164–167.
- [261] G.A. Stefanatos, J. Wasserstein, Attention deficit/hyperactivity disorder as a right hemisphere syndrome. Selective literature and detailed neuropsychological case studies, *Ann. NY Acad. Sci.* 931 (2001) 172–195.
- [262] S.C. Steffensen, M.C. Wilson, S.J. Henriksen, Coloboma contiguous gene deletion encompassing Snap alters hippocampal plasticity, *Synapse* 22 (1996) 281–289.
- [263] A.P. Streissguth, H.M. Barr, D.C. Martin, Alcohol exposure in utero and functional deficits in children during the first four years of life, *Ciba Found. Sympos.* 105 (1984) 176–196.
- [264] A.P. Streissguth, F.L. Bookstein, P.D. Sampson, H.M. Barr, Attention: Prenatal alcohol and continuities of vigilance and attentional problems from 4 through 14 years, *Dev. Psychopathol.* 7 (1995) 419–446.
- [265] D.T. Stuss, C.A. Gow, C.R. Hetherington, 'No longer Gage': frontal lobe dysfunction and emotional changes, *J. Consult. Clin. Psychol.* 60 (1992) 349–359.
- [266] J.M. Swanson, P. Flodman, J.L. Kennedy, M.A. Spence, R. Moyzis, S. Schuck, M. Murias, J. Moriarty, C. Barr, M. Smith, M. Posner, Dopamine genes and ADHD, *Neurosci. Biobehav. Rev.* 24 (2000) 21–25.
- [267] J.M. Swanson, S. Gupta, D. Guinta, D. Flynn, D. Agler, M. Lerner, L. Williams, I. Shoulson, S. Wigal, Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children, *Clin. Pharmacol. Ther.* 66 (1999) 295–305.
- [268] J.M. Swanson, M. Posner, S. Potkin, S. Bonforte, D. Youpa, C. Fiore, D. Cantwell, F. Crinella, Activating tasks for the study of visual-spatial attention in ADHD: a cognitive anatomic approach, *J. Child Neurol.* 6 (1991) S119–127.
- [269] J.M. Swanson, G.A. Sunohara, J.L. Kennedy, R. Regino, E. Fineberg, T. Wigal, M. Lerner, L. Williams, G.J. LaHoste, S. Wigal, Association of the dopamine receptor D₄ (DRD4) gene with a refined phenotype of attention deficit hyperactivity disorder (ADHD): a family-based approach, *Mol. Psychiatry* 3 (1998) 38–41.
- [270] J.M. Swanson, N.D. Volkow, Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD, *Behav. Brain Res.* 130 (2002) 73–78.
- [271] M. Takasuna, T. Iwasaki, Active and passive avoidance learning in rats neonatally treated with intraventricular 6-hydroxydopamine, *Behav. Brain Res.* 74 (1996) 119–126.
- [272] E. Taylor, Clinical foundations of hyperactivity research, *Behav. Brain Res.* 94 (1998) 11–24.
- [273] C.E. Tedford, M. Hoffmann, N. Seyedi, N. Maruyama, R. Levi, S.L. Yates, S.M. Ali, J.G. Phillips, High antagonistic potency of GT-2227 and GT-2331, new histamine H₂ receptor antagonists, in two functional models, *Eur. J. Pharmacol.* 351 (1998) 307–311.
- [274] M.H. Teicher, N.I. Barber, J. Reichheld, R.J. Baldessarini, Selective depletion of cerebral norepinephrine with 6-hydroxydopamine and GBR-12909 in rat, *Dev. Brain Res.* 30 (1986) 124–128.
- [275] R.D. Todd, Genetics of attention deficit/hyperactivity disorder: Are we ready for molecular genetic studies?, *Am. J. Med. Genet.* 96 (2000) 241–243.

- [276] R.D. Todd, Y.J. Jong, E.A. Lobos, W. Reich, A.C. Heath, R.J. Neuman, No association of the dopamine transporter gene 3'VNTR polymorphism with ADHD subtypes in a population sample of twins, *Am. J. Med. Genet.* 105 (2001) 745–748.
- [277] R.D. Todd, R.J. Neuman, E.A. Lobos, Y.J. Jong, W. Reich, A.C. Heath, Lack of association of dopamine D₄ receptor gene polymorphisms with ADHD subtypes in a population sample of twins, *Am. J. Med. Genet.* 105 (2001) 432–438.
- [278] A.C. Towle, H.E. Criswell, E.H. Maynard, J.M. Lauder, T.H. Joh, R.A. Mueller, G.R. Breese, Serotonergic innervation of the rat caudate following a neonatal 6-hydroxydopamine lesion: an anatomical, biochemical and pharmacological study, *Pharmacol. Biochem. Behav.* 34 (1989) 367–374.
- [279] D.G. Ullman, R.A. Barkley, H.W. Brown, The behavioral symptoms of hyperkinetic children who successfully responded to stimulant drug treatment, *Am. J. Orthopsychiatry* 48 (1978) 425–437.
- [280] U. Ungerstedt, Adipsia and aphagia after 6-hydroxydopamine-induced degeneration of the nigrostriatal dopamine system, *Acta Physiol. Scand. Suppl.* 367 (1971) 95–122.
- [281] C.H. van Dyck, D.M. Quinlan, L.M. Cretella, J.K. Staley, R.T. Malison, R.M. Baldwin, J.P. Seibyl, R.B. Innis, Unaltered dopamine transporter availability in adult attention deficit-hyperactivity disorder, *Am. J. Psychiatry* 159 (2002) 309–312.
- [282] H.H. van Tol, C.M. Wu, H.C. Guan, K. Ohara, J.R. Bunzow, O. Civelli, J. Kennedy, P. Seeman, H.B. Niznik, V. Jovanovic, Multiple dopamine D₄ receptor variants in the human population, *Nature* 358 (1992) 149–152.
- [283] D. Viggiano, A.G. Sadile, Hypertrophic A10 dopamine neurones in a rat model of attention-deficit hyperactivity disorder (ADHD), *Neuroreport* 11 (2000) 3677–3680.
- [284] N.D. Volkow, G.J. Wang, J.S. Fowler, J. Logan, D. Franceschi, L. Maynard, Y.S. Ding, S.J. Gatley, A. Gifford, W. Zhu, J.M. Swanson, Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications, *Synapse* 43 (2002) 181–187.
- [285] D. Wahlsten, P.M. Schalomon, A new hybrid mouse model for agenesis of the corpus callosum, *Behav. Brain Res.* 64 (1994) 111–117.
- [286] D.M. Warburton, K. Wesnes, Drugs as research tools in psychology: cholinergic drugs and information processing, *Neuropsychobiology* 11 (1984) 121–132.
- [287] F.B. Weilmüller, J.P. Bruno, Drinking behavior and motor function in rat pups depleted of brain dopamine during development, *Dev. Psychobiol.* 22 (1989) 101–113.
- [288] I.Q. Whishaw, D.R. Funk, S.J. Hawryluk, E.D. Karbasheski, Absence of sparing of spatial navigation, skilled forelimb and tongue use and limb posture in the rat after neonatal dopamine depletion, *Physiol. Behav.* 40 (1987) 247–253.
- [289] S. Whitmont, C. Clark, Kinaesthetic acuity and fine motor skills in children with attention deficit hyperactivity disorder: a preliminary report, *Dev. Med. Child Neurol.* 38 (1996) 1091–1098.
- [290] T.E. Wilens, J. Biederman, T.J. Spencer, Attention deficit/hyperactivity disorder across the lifespan, *Annu. Rev. Med.* 53 (2002) 113–131.
- [291] T.E. Wilens, J. Biederman, T.J. Spencer, J. Bostic, J. Prince, M.C. Monuteaux, J. Soriano, C. Fine, A. Abrams, M. Rater, D. Polisner, A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder, *Am. J. Psychiatry* 156 (1999) 1931–1937.
- [292] A.J. Wilkins, T. Shallice, R. McCarthy, Frontal lesions and sustained attention, *Neuropsychologia* 25 (1987) 359–365.
- [293] M.C. Wilson, Coloboma mouse mutant as an animal model of hyperkinesia and attention deficit hyperactivity disorder, *Neurosci. Biobehav. Rev.* 24 (2000) 51–57.
- [294] K. Wisniewski, J.S. Jeret, Callosal agenesis: review of clinical, pathological, and cytogenetic features, in: M. Lassonde, M.A. Jeeves (Eds.), *Callosal Agenesis: A Natural Split-Brain*, Plenum Press, New York, 1994, pp. 1–6.
- [295] D.L. Woods, R.T. Knight, Electrophysiologic evidence of increased distractibility after dorsolateral prefrontal lesions, *Neurology* 36 (1986) 212–216.
- [296] R.S. Wool, D.A. Weldon, B.A. Shaywitz, G.M. Anderson, D.J. Cohen, M.H. Teicher, Amphetamine reverses learning deficits in 6-hydroxydopamine-treated rat pups, *Dev. Psychobiol.* 20 (1987) 219–232.
- [297] A.H. Wong, C.E. Buckle, H.H. van Tol, Polymorphisms in dopamine receptors: what do they tell us?, *Eur. J. Pharmacol.* 410 (2000) 183–203.
- [298] J.M. Wyss, G. Fisk, T. van Groen, Impaired learning and memory in mature spontaneously hypertensive rats, *Brain Res.* 592 (1992) 135–140.
- [299] C. Xu, R. Schachar, R. Tannock, W. Roberts, M. Malone, J.L. Kennedy, C.L. Barr, Linkage study of the alpha-2A adrenergic receptor in attention-deficit hyperactivity disorder families, *Am. J. Med. Genet.* 105 (2001) 159–162.
- [300] F. Xu, R.R. Gainetdinov, W.C. Wetsel, S.R. Jones, L.M. Bohn, G.W. Miller, Y.M. Wang, M.G. Caron, Mice lacking the norepinephrine transporter are supersensitive to psychostimulants, *Nat. Neurosci.* 3 (2000) 465–471.
- [301] A.J. Zametkin, J.L. Rapoport, Neurobiology of attention deficit disorder with hyperactivity: where have we come in 50 years?, *J. Am. Acad. Child Adolesc. Psychiatry* 26 (1987) 676–686.
- [302] A.J. Zametkin, J.L. Rapoport, Noradrenergic hypothesis of attention deficit disorder with hyperactivity: A critical review, in: H.Y. Meltzer (Ed.), *Psychopharmacology: The Third Generation of Progress*, Raven Press, New York, 1987, pp. 37–842.
- [303] M. Zappitelli, T. Pinto, N. Grizenko, Pre-, peri-, and postnatal trauma in subjects with attention-deficit hyperactivity disorder, *Can. J. Psychiatry* 46 (2001) 542–548.
- [304] K. Zhang, E. Davids, F.I. Tarazi, R.J. Baldessarini, Effects of dopamine D₄ receptor-selective antagonists on motor hyperactivity in rats with neonatal 6-hydroxydopamine lesions, *Psychopharmacology* 161 (2002) 100–106.
- [305] K. Zhang, E. Davids, F.I. Tarazi, R.J. Baldessarini, Serotonin transporter binding increases in caudate-putamen and nucleus accumbens after neonatal 6-hydroxydopamine lesions in rats: Implications for motor hyperactivity, *Dev. Brain Res.* 137 (2002) 135–138.
- [306] K. Zhang, F.I. Tarazi, R.J. Baldessarini, Role of dopamine D₄ receptors in motor hyperactivity induced by neonatal 6-hydroxydopamine lesions in rats, *Neuropsychopharmacology* 25 (2001) 624–632.
- [307] K. Zhang, F.I. Tarazi, E. Davids, R.J. Baldessarini, Plasticity of dopamine D₄ receptors in rat forebrain: temporal association with motor hyperactivity following neonatal 6-hydroxydopamine lesioning, *Neuropsychopharmacology* 26 (2002) 625–633.
- [308] M.J. Zigmond, E.M. Stricker, Recovery of feeding and drinking by rats after intraventricular 6-hydroxy-dopamine or lateral hypothalamic lesions, *Science* 182 (1973) 717–720.